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ECZEMA AND ESSENTIAL FATTY ACIDS

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DERMATOLOGIC conditions classified perforce under the comprehensive and admittedly unsatisfactory term "eczema" constitute one of the chief problems encountered in the practice of medicine. True enough, as diagnostic methods have improved, the number of clinical conditions so designated has become fewer. Nevertheless, the various types of chronic dermatitis commonly classified as eczema must be included in such a study as that reported here. The primary purpose of this paper is to present evidence for a possible relationship between a disturbance in essential fatty acid metabolism and the occurrence of eczema.

FACTORS CONCERNED WITH THE NORMAL INTEGRITY OF THE SKIN

In light of the many significant advances made in the field of nutrition during the last two decades, it is rather remarkable that relatively little is known regarding the nutritional factors which are responsible for maintenance of a healthy skin. One of the most notable contributions to the knowledge on this subject was the work of Burr and Burr [1]

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1. Burr, G. O., and Burr, M. M.: A New Deficiency Disease Produced by Rigid Exclusion of Fat from Diet, J. Biol. Chem. **82**:345 (May) 1929; On Nature and Role of Fatty Acids Essential in Nutrition, ibid. **86**:587 (April) 1930. Burr, G. O.; Burr, M. M., and Miller, E. S.: On the Fatty Acids Essential in Nutrition ibid. **97**:1 (July) 1932.

which disclosed the essential nature of the highly unsaturated fatty acids, particularly linoleic acid and arachidonic acid. These dietary substances were found to be required in the rat, not only for growth and reproduction, but also for preservation of the integrity of the skin. Hansen and Wiese [2] subsequently showed that when young dogs were reared on diets extremely low in fat their hair became dry and coarse and the skin showed dryness and flaky desquamation, whereas litter mates of these animals, receiving fresh lard as a substitute for sucrose, had skin of a normal soft texture. It has also been shown [3] that the inclusion of highly unsaturated fatty acids in the diet will prevent the development in experimental animals of the cutaneous eruptions which characterize pyridoxine (vitamin B_6) deficiency. It is yet to be demonstrated, however, that the fatty acids known to be essential for experimental animals are required in human nutrition.[4]

The first indication that the unsaturated fatty acids might be of importance in human nutrition was gained from observations on patients with infantile eczema. In a preliminary clinical study, it was found by Hansen [5] that certain infants afflicted with this disease appeared to be benefited when vegetable oils rich in unsaturated fatty acids were added to the diet in comparatively large amounts. This led to a study of the blood lipids as well as to further attempts at clinical evaluation. Cornbleet [6] in 1935 reported gratifying results from the use of corn oil in the treatment of 87 patients with eczema. Finnerud, Kesler and Wiese [7] used fresh lard as a source of unsaturated fatty acids for the treatment of eczema in a group of older children and adults. They have commented that a satisfactory response was evidenced in more than one half of their group. In a much smaller series, Ginsberg and Bernstein [8] also reported favorable results for 4 out of 6 infants and

2. Hansen, A. E., and Wiese, H. F.: Studies with Dogs Maintained on Diets Low in Fat, Proc. Soc. Exper. Biol. & Med. **52**:205 (March) 1943.

3. Salmon, W. D.: The Effect of Certain Oils in Alleviating Localized Erythematous Dermatitis (Acrodynia or Vitamin B_6 Deficiency) in Rats, J. Biol. Chem. **123**:civ, 1938.

4. The present status of this subject has recently been reviewed by Hansen and Burr at the request of the Council on Foods and Nutrition of the American Medical Association.

5. Hansen, A. E.: Serum Lipid Changes and Therapeutic Effects of Various Oils in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **31**:160 (Nov.) 1933.

6. Cornbleet, T.: Use of Maize Oil (Unsaturated Fatty Acids) in the Treatment of Eczema: Preliminary Report, Arch. Dermat. & Syph. **31**:224 (Feb.) 1935.

7. Finnerud, C. W.; Kesler, R. L., and Wiese, H. F.: Ingestion of Lard in the Treatment of Eczema and Allied Dermatoses, Arch. Dermat. & Syph. **44**: 849, (Nov.) 1941.

8. Ginsberg, J. E., and Bernstein, C.: Effect of Oils Containing Unsaturated Fatty Acids on Patients with Dermatitis, Arch. Dermat. & Syph. **36**:1033 (Nov.) 1937.

3 out of 11 adults who were given vegetable oils. Epstein and Glick [9] had a good response in only 2 of 8 adolescents and no improvement in 2 infants. Taub and Zakon [10] have reported negative results for a series of 8 infants, 2 of whom had complications of cysts and furunculosis and 1 of whom was also asthmatic. The present report deals with data derived from a more extensive investigation of the problem undertaken to determine the true significance of the nutritional role played by the unsaturated fatty acids in clinical eczema.

MATERIAL AND METHODS

Organization of Clinical Studies.—Patients: A total of 225 patients with eczema have been seen during the course of this study. Most of them were observed as outpatients or as hospital patients at the University of Minnesota, but additional studies were made in the department of Pediatrics at Yale University and at the University of Texas. Only a few were private patients. The age distribution of the whole series was as follows: 123 patients under 2 years, 67 patients between 2 and 15, and 35 patients 16 years of age or over. They were divided about equally according to sex. No attempt was made to select patients other than to study those with an intractable cutaneous eruption of the eczematoid dermatitis type.

Records: The usual difficulty was encountered in interpretation and evaluation of the clinical condition from day to day and the over-all progress from week to week. The record of 1 patient, for example, who was followed in both the dermatologic and the pediatric outpatient clinic, had notations of "improved" twenty-six times, "about the same" five times, and "worse" only three times, but he still had an extensive eczematous eruption at the end of a five year period. In an attempt to reduce interpretative errors of this type to a minimum special record forms were constructed to facilitate an objective check on the type and severity of the eruption as well as to note its anatomic distribution. In addition, photographic evidence was utilized, although the limitations of this were recognized. Even with these precautions the empiric character of the observations probably influenced the results to a certain extent, but the use of the standardized forms undoubtedly permitted more accurate recording than was possible when only written statements were employed. The records and photographs of a representative case are presented in figures 1, 2 and 3 to illustrate the development of the technic for following our patients.

9. Epstein, N. N., and Glick, D.: Unsaturated Fatty Acids in Eczema: Observations on Acne Vulgaris, Psoriasis, Xanthoma Tuberosum, and Xanthoma Palpebrarum, Arch. Dermat. & Syph. **35**:427 (March) 1937.

10. Taub, S. J., and Zakon, S. J.: Use of Unsaturated Fatty Acids in Treatment of Eczema (Atopic Dermatitis, Neurodermatitis), J. A. M. A. **105**:1675 (Nov. 23) 1935.

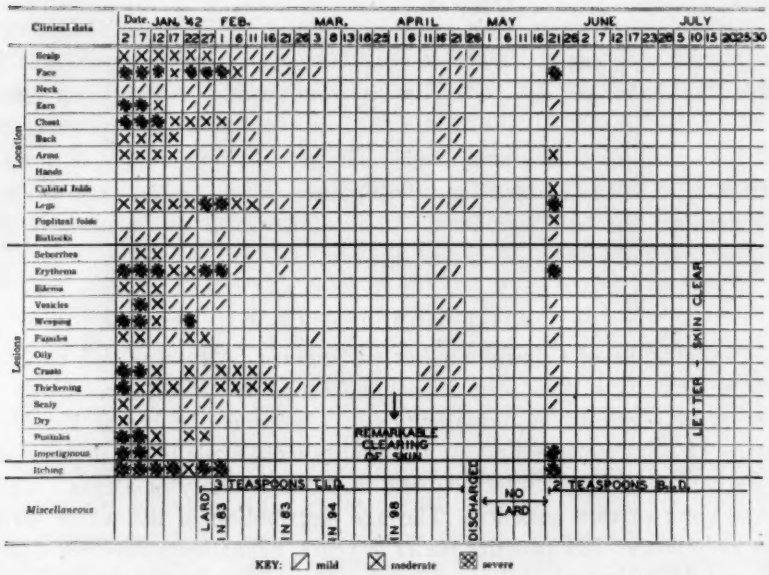

Fig. 1.—Record of periodic examinations of patient D. C., whose condition had been diagnosed as infantile eczema.

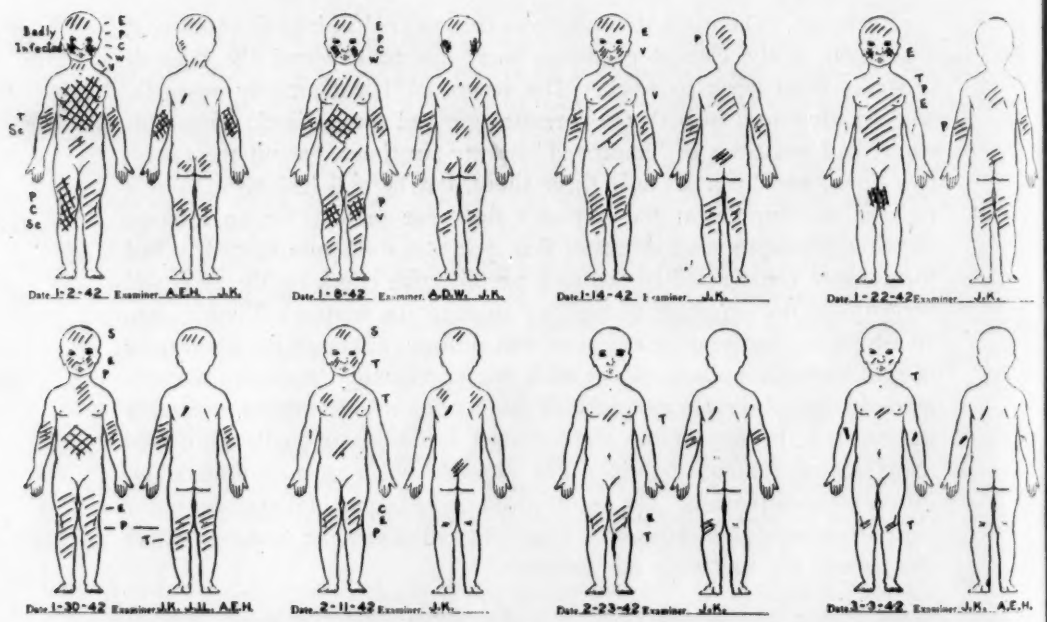
Badly Infected
Date 1-2-42 Examiner A.E.H. J.K.
Date 1-8-42 Examiner A.D.W. J.K.
Date 1-14-42 Examiner J.K.
Date 1-22-42 Examiner J.K.
Date 1-30-42 Examiner J.K. J.H. A.E.H.
Date 2-11-42 Examiner J.K.
Date 2-23-42 Examiner J.K.
Date 3-9-42 Examiner J.K. A.E.H.

Fig. 2.—Anatomic distribution of lesions at periodic examinations of patient D. C. The key for the letters is as follows: *C*, crusts; *E*, erythema; *P*, pustules; *S*, seborrhea; *T*, thickening; *V*, vesicles, and *W*, weeping.

Clinical Approach: It was virtually impossible to conduct such a study as this by the approved scientific approach of using alternate cases for special treatment. Therefore, preliminary "control periods," usually of four or more weeks, were used for observation and a "clinical base line" was established before any distinct change was made in the therapeutic regimen. Both local therapy and diet were kept as nearly as possible to that of the preceding regimen when any new procedure was being evaluated. The local measures were kept as simple as possible and included restraints; wet packs of saline solution, solution of boric

Fig. 3.—Photographic record of clinical response of patient D. C. *A*, photograph taken Jan. 24, 1942. *B*, photograph taken April 1.

acid or solution of aluminum acetate, and ointments of boric acid, zinc paste or ammoniated mercury as indicated, with preparations of salicylic acid and sulfur, or resorcinol, for infant scalps when needed. Because of the recognized effectiveness of crude coal tar preparations these were avoided except for special circumstances.

Use of Fats: In order to evaluate their possible therapeutic implications, certain fats rich in unsaturated fatty acids have been included in the diets of patients with resistant eczema. Fresh lard, approximately 1 to 2 ounces (about 30 to 60 Gm.) daily has been used for the largest series of patients. Usually at the outset 1 teaspoon was prescribed for each meal.

This amount was increased gradually to 2 and then to 3 teaspoons three times daily for the larger children or more difficult cases. The largest amount administered was 1 ounce thrice daily. In most instances no difficulty was encountered in accustoming the patient to take this much fresh lard, and infants often licked it directly from the spoon. For other patients it was mixed with sugar, peanut butter, cinnamon, or jam and served with cereal, as a palatable spread for crackers or as a sandwich. Similar amounts were used when vegetable fats such as raw linseed oil or corn oil were the dietary sources of the unsaturated fatty acids. These particular fats were selected because Burr [11] had found them to be superior sources of the essential fatty acids in animal experimentations. In a few instances emulsions of unsaturated fatty acids were used. However, esters of linoleic and arachidonic acids have not been available for extensive clinical trial. In a few cases in which known sensitivities existed elimination of the offending dietary constituents preceded addition of the supplementary fat.

Duration of Treatment: Usually clinical evaluataion could be made within one to two months after introducing the fat into the diet, but more often the therapeutic measure was continued unchanged for at least two or three months to insure more reliable interpretation. In some instances, in which the smaller amounts of dietary fat were used, the therapeutic trial period was continued for a longer time.

Studies of Blood Lipids.—Blood lipids were studied in 171 of the patients with eczema and in 101 control subjects. The impetus for such studies was the finding in earlier work [12] that the serum fatty acids of patients with eczema tend to be less unsaturated than those of control subjects. The earliest observations were made by determining the total iodine absorbed by the blood serum. This procedure was later replaced by determination of fatty acids by the oxidative method. In an attempt to obtain more detailed information concerning the lipids of the blood, a microgravimetric technic [13] was devised by which the average length of the fatty acid chains, as well as the iodine number of the separated fatty acid fractions, can be determined.[14] Adaptation of this principle

11. Burr, G. O.; Brown, J. B.; Kass, J. P., and Lundberg, W. O.: Comparative Curative Values of Unsaturated Fatty Acids in Fat Deficiency, Proc. Soc. Exper. Biol. & Med. **44**:242 (May) 1940.

12. Hansen, A. E.: Study of Iodine Number of Serum Fatty Acids in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **30**:1198 (June) 1933; Serum Lipids in Eczema and in Other Pathologic Conditions, Am. J. Dis. Child. **53**:933 (April) 1937.

13. Wilson, W. R., and Hansen, A. E.: Study of Serum Lipids by Microgravimetric Technique, J. Biol. Chem. **112**:457 (Jan.) 1936.

14. Hansen, A. E.: Nature of Fatty Acids of Acetone Insoluble (Phospholipid) Fraction of Serum, Proc. Soc. Exper. Biol. & Med. **40**:376 (March) 1939.

makes it possible to determine the nature of two fatty acid fractions, the acetone-insoluble (phospholipids) and the acetone-soluble (triglyceride and cholesterol-ester fatty acids). In the present paper we shall present only the data in regard to iodine numbers of the total fatty acids of the serum, and shall attempt to correlate these observations with the clinical response to the administration of fats rich in unsaturated fatty acids.

PRESENTATION OF RESULTS

Clinical Evaluation.—We have summarized the clinical response of 181 of the patients in figure 4, and have grouped the results according to age and in relation to the type of therapy. The clinical responses of our patients have been evaluated as follows: (1) good, where the

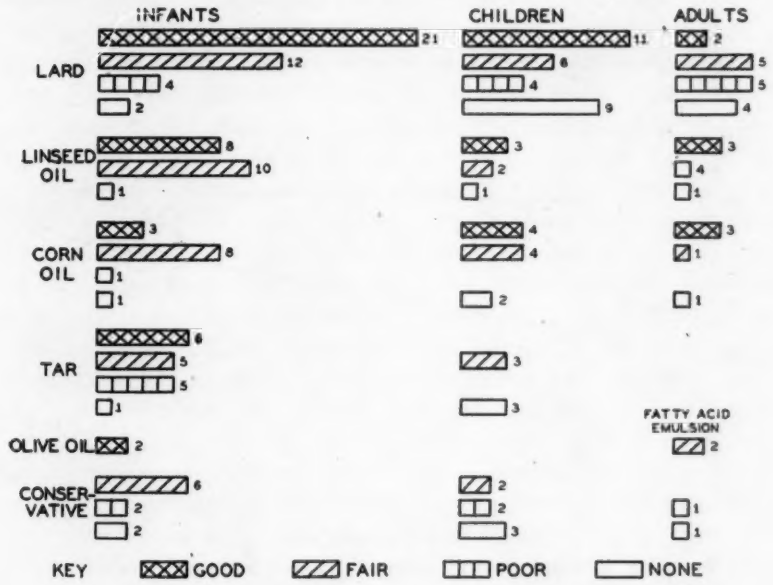

Fig. 4.—Clinical response of 181 patients with eczema.

cutaneous manifestations either completely disappeared or nearly cleared; (2) fair, when definite evidence of improvement was present; (3) poor, when improvement was only slight, and (4) none, when no change occurred in the clinical condition.

Of the 148 patients receiving some form of unsaturated fatty acids there were 60 in whom the results were good to excellent; 51 in whom results were fair to good, and 37 whose response was either poor or lacking. In those in whom there was either slight or no evidence of improvement, the most unsatisfactory results were in the older age groups, since the progress of 40 per cent of the adults was classified as "poor to none," in contrast to 36 per cent of the children and only

12 per cent of the infants. The number of persons receiving each type of fatty acid therapy is too small for statistical evaluation, but a higher percentage of those on the lard regimen were in the "good to excellent" group. Preparations of crude coal tar were used as the only form of specific therapy for 24 of the patients with intractable eczema. The infants responded somewhat better than the older children, but results among the infants were nearly equally divided among the "poor," "fair" and "good" evaluations. Conservative therapeutic measures such as nonspecific local therapy or elimination diets alone were used for 19 patients with fair results in 8 and no response in 6. There were 20 of our patients with whom the cooperation was too poor for any evalua-

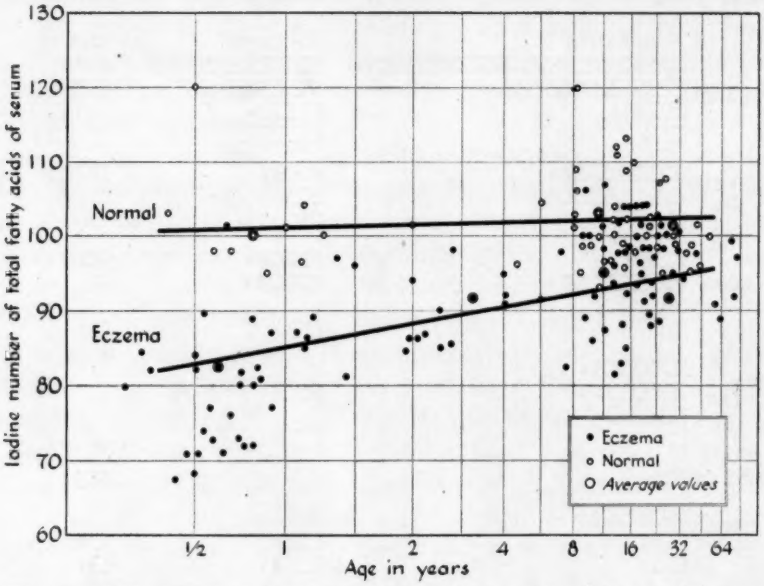

Fig. 5.—Iodine numbers of fatty acids of the serum in patients with eczema and in control subjects.

tion. An additional 23 patients, chiefly adults, were included in the series for analyses of their serum lipids only.

Observations Concerning Serum Lipids.—Initial Iodine Numbers: There have been a total of 380 determinations of the blood lipids for patients with eczema and 122 determinations for control subjects. In a previous publication [12] the difference in the average iodine number of the fatty acids of the serum between these two groups was found to be statistically significant, and a similar trend in results has been observed in subsequent studies. In figure 5 are presented representative data from our own laboratory as well as data from Finnerud, Kesler and Wiese, who also employed the microgravimetric technic. The lower degree of unsaturation for the fatty acids of the blood serum of patients

with eczema is at once apparent from this figure. This finding appears to be especially characteristic of eczema in the younger age group. In our entire series of patients with active eczema we have found that 82 per cent of the infants under 2 years of age, 74 per cent of the children between 2 and 15 years inclusive, and 55 per cent of the adults have had iodine numbers which fell below the normal range. A similar low degree of unsaturation for the serum of patients with eczematoid dermatitis has been reported by Faber and Roberts.[15] Decreased iodine numbers have been found for adults by Finnerud and his co-workers, by Stoesser[16] for infants, and by Schornstein[17] for children. Ginsberg and Bernstein stated that average iodine values are unchanged for patients with cutaneous disorders, but they did not include any individual values in their report. Epstein and Glick were unable to find any differences between eczematous and normal subjects in regard to iodine numbers, but they worked with whole blood rather than with blood serum. A pertinent observation made in studies of blood lipids of experimental animals on fat-free diets was that there was a small range for the iodine numbers for whole blood in contrast to a wide range for the plasma or serum lipids.[18] In determinations on pooled samples of human serum, Brown and Hansen[19] found smaller amounts of linoleic and arachidonic acids for patients with eczema than for normal subjects.

Fractionation of Serum Lipids: We have attempted to develop methods to help clarify the metabolic role of these unsaturated fatty acids, and have tried to determine which fraction of the blood lipids is involved in the alteration in the iodine number which occurs more or less characteristically in patients with eczema. A previous report[14] indicated that the relatively low degree of unsaturation of the phospholipid fatty acids was not sufficient to account for the low iodine numbers observed in these patients. Subsequent study has indicated that a great decrease in the iodine number was found in the acetone-soluble fraction, which includes the triglyceride and cholesterol-ester fatty acids. More recently Wiese and Hansen[20] found in experimental animals on

15. Faber, H. K., and Roberts, D. B.: Studies in Infantile Allergic Eczema: Serum Lipids, with Special Reference to Saturation of the Fatty Acids, J. Pediat. **6**:490 (April) 1935.

16. Stoesser, A. V.: Proc. Soc. Exper. Biol. & Med., to be published.

17. Schornstein, L.: Ueber den Gehalt der Serumfette an ungesättigten Fettsäuren beim Säuglingsekzem, Ztschr. f. Kinderh. **59**:52, 1937.

18. Miller, E. V., and Hansen, A. E.: Effect of Low Fat Diet on Lipids of Erythrocytes, Plasma, Serum and Whole Blood of Dogs, Proc. Soc. Exper. Biol. & Med. **56**:244 (June) 1944.

19. Brown, W. R., and Hansen, A. E.: Arachidonic and Linolic Acid of Serum in Normal and Eczematous Human Subjects, Proc. Soc. Exper. Biol. & Med. **36**:113 (March) 1937.

20. Wiese, H. F., and Hansen, A. E.: Distribution of Fatty Acids in the Blood Serum of Dogs as Affected by Diet, Federation Proc. **3**:97 (March) 1944.

fat-free diets, by means of enzymatic hydrolysis of the acetone-soluble fraction, that the greatest decrease in the iodine number occurred in the cholesterol-ester fatty acids. The method used, however, requires too much blood and is too cumbersome for clinical application, so that better technics are needed before the significance of the essential fatty acids can be completely understood.

Changes in Iodine Numbers During Treatment: Periodic findings for the iodine numbers of the serum lipids for all patients in the lard, linseed oil, corn oil, and tar series for whom such follow-up studies are available are graphically recorded in figures 6, 7 and 8. It is quite apparent that with the administration of fats rich in unsaturated fatty

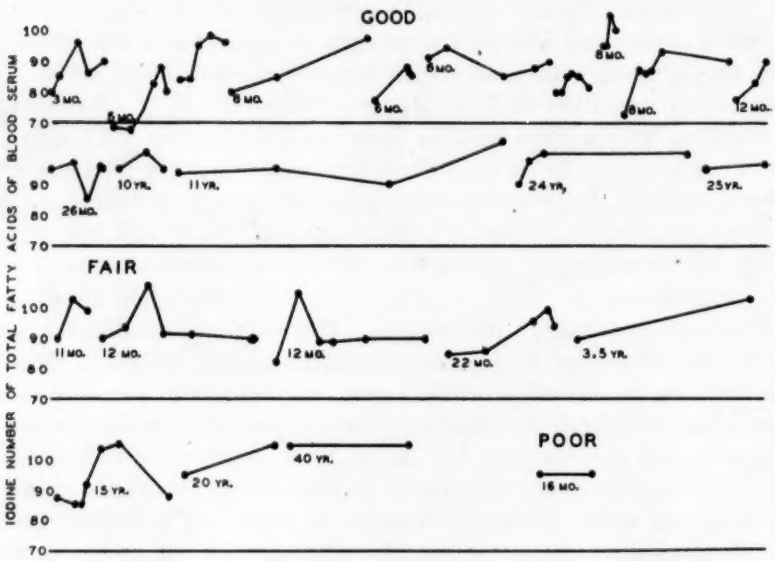

Fig. 6.—Relationship between iodine numbers and clinical response: results with lard.

acids the iodine numbers of the serum fatty acids tended to rise. As might be expected, the increases in iodine number were greatest in those patients receiving the vegetable oils, undoubtedly because of the high iodine numbers of these oils. Finnerud and his co-workers also found that, in general, when lard was added to the diet of patients with eczema the change in iodine number corresponded to the improvement in clinical condition. Our data indicate a similar tendency. When patients 1 year of age or under are considered, there was a much greater uniformity in response and the increase in iodine numbers for the serum fatty acids corresponded rather well with the improvement in the skin. In this connection it is well to point out the finding of Wiese, Hansen and

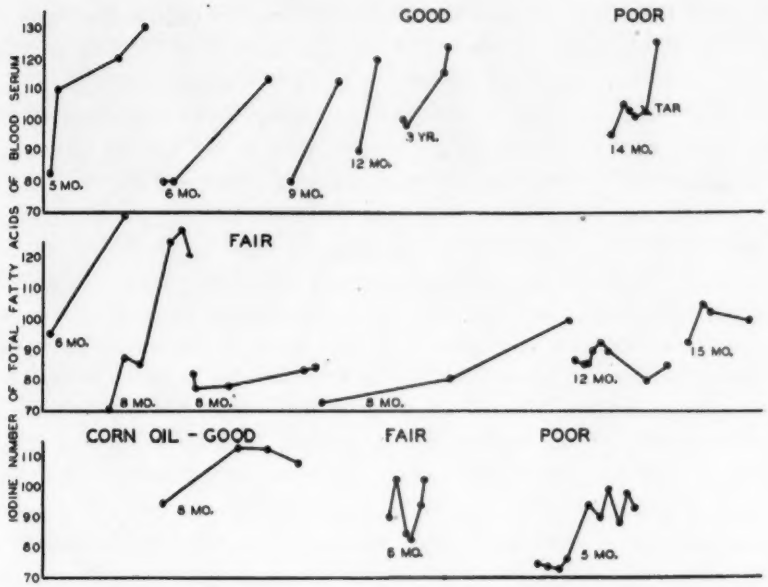

Fig. 7.—Relationship between iodine numbers and clinical response: results with raw linseed and corn oil.

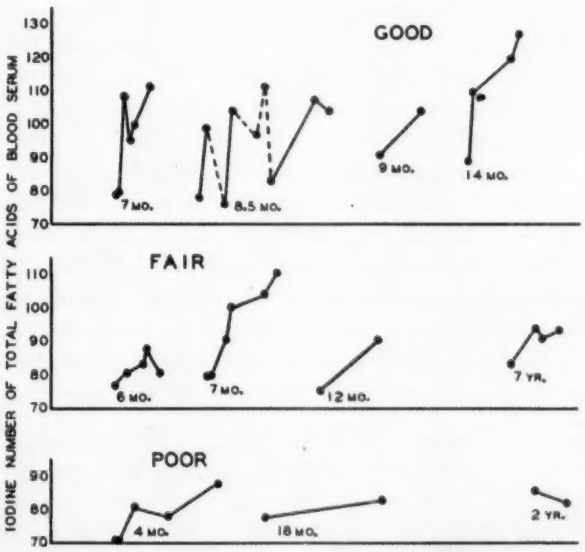

Fig. 8.—Relationship between iodine numbers and clinical response: results with tar.

Miller [21] that for dogs suffering from the fat deficiency syndrome, the increases in iodine numbers for the serum may lag behind the improvement noted in their skin depending on the amount of fresh lard added to the diet. In a current report, Stoesser [16] states that of 11 infants suffering with weeping eczema all had progressive increases in the iodine numbers which paralleled improvement of the eczema when they were given milk substitute formulas prepared from soy beans.

The prompt rise in iodine numbers of the serum fatty acids of patients treated with preparations of crude coal tar may be explained in part by the fact that some of the determinations were made with the oxidative technic which leads to high values, but nonetheless there would appear to be a true increase in unsaturated fatty acids in the serum under this form of therapy. The explanation for this response is no more apparent now than when the original observation was made, but the increase in iodine number of the serum fatty acids may lend some support to the theory [22] that tar preparations affect the lipid metabolism of the tissues. It is hoped that the development of accurate methods for determination of specific unsaturated fatty acids will permit a better interpretation of these data in terms of the interrelationships in lipid metabolism between the eczematous tissues and the blood serum.

COMMENT

Significance of Low Iodine Numbers for the Serum Lipids.—Diet: In interpreting the low iodine numbers found in patients with eczema, several explanations are possible. It has been demonstrated [23] that the content of linoleic and arachidonic acids in the blood serum is lowered when a human subject is maintained for a prolonged period on a diet low in fat. We therefore have been careful throughout our studies to have the control diets of our patients essentially normal. This was especially important in view of the common practice of giving eczematous infants diets low in fat. Likewise standardized control of the dietary fat was necessary, since certain eczematous infants had previously received milk substitute diets for a short time which contained fats relatively high in unsaturated fatty acids.

Another factor to be considered in explanation of the low iodine numbers for the serums of these infants is the relatively low content of

21. Wiese, H. F.; Hansen, A. E., and Miller, E. V. O.: Effect of Addition of Lard to a Low Fat Diet in Dogs, Federation Proc. **3**:94 (March) 1944.

22. Haendel, M., and Malet, J.: Ueber die Beziehungen des Geschwulstwachstums zur Ernährung und zum Stoffwechsel: Teerpinselung und Gewebslipoide, Ztschr. f. Krebsforsch. **29**:324, 1929.

23. Brown, W. R.; Hansen, A. E.; Burr, G. O., and McQuarrie, I.: Effects of Prolonged Use of Extremely Low-Fat Diet on Adult Human Subject, J. Nutrition **16**:511 (Dec.) 1938.

essential fatty acids in cows' milk.[24] We must point out, however, that our control subjects were infants of the same age group and were fed artificial formulas comparable to the feedings for the infants with eczema. In this connection it is of interest to comment on the appreciable amounts of linoleic and arachidonic acids present in human milk, and call attention to the observation of Grulee and Sanford[25] that eczema occurs seven times as frequently in artificially fed infants as in those maintained on breast milk. Robinson[26] also has reported that cutaneous eruptions are more frequent in artificially fed infants. On the basis of a rather small number of data, we have found that the content of highly unsaturated acids was somewhat less in the milk of mothers nursing eczematous infants than in the milk of mothers with normal infants.

Absorption: A second possible explanation of a low iodine number for the serum fatty acids might be a defective absorption of ingested fat, for Luzzatti and Hansen[27] have shown that in cases of the celiac syndrome there is a lower degree of unsaturation for the serum fatty acids. In this connection an observation which may be pertinent is the report of Bennett, Hunter and Vaughan[28] regarding the presence of cutaneous eruptions in 7 cases of idiopathic steatorrhea. These authors state, "the frequent occurrence of skin lesions appears too striking to be mere coincidence." Other authors[29] have also noted the frequent occurrence of dermatologic disorders among patients with low fat intakes or impaired absorption of fat. To test the possibility of faulty absorption of fat in patients with eczema, several infants were given test meals of 4 ounces (113.4 Gm.) of 40 per cent cream followed by periodic analyses of the serum fatty acids for the subsequent twelve hours. Figure 9 illustrates the data for one of these patients. It will be noted that absorption of fat was normal, the iodine number of the serum

24. Hilditch, T. P., and Meara, M. L.: Human-Milk Fat: I. Component Fatty Acids, Biochem. J. **38**:29, 1944; II. Component Glycerides, ibid. **38**:437, 1944.

25. Grulee, C. G., and Sanford, H. N.: Influence of Breast and Artificial Feeding on Infantile Eczema, J. Pediat. **9**:223 (Aug.) 1936.

26. Robinson, E. C.: Study of 240 Breast Fed and Artificially Fed Infants in St. Louis Area: Incidence of Rashes and Gastrointestinal Disturbances in Breast-Fed Infants and Infants Fed on Fresh Milk Formulas and on Acidified (Lactic Acid) and Nonacidified Evaporated Milk Formulas, Am. J. Dis. Child. **59**:1002 (May) 1940.

27. Luzzatti, L., and Hansen, A. E.: Study of Serum Lipids in the Celiac Syndrome, J. Pediat. **24**:417 (April) 1944.

28. Bennett, T. I.; Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease): Nutritional Disturbance Associated with Tetany, Osteomalacia, and Anemia, Quart. J. Med. **1**:603 (Oct.) 1932.

29. Konstam, G., and Gordon, H.: Idiopathic Steatorrhoea with Skin Lesions and Megalocytic Anaemia, Proc. Roy. Soc. Med. **29**:629 (April) 1936. Riley, I. D.: Metabolic Eczema in Idiopathic Steatorrhoea, Lancet **1**:262 (Feb. 4) 1939.

fatty acids decreasing in proportion to the degree of unsaturation of the cream fat. Freudenberg and Schornstein [30] likewise have presented data to show that infants with eczema have no difficulty in absorbing ingested fat. To guard against the possibility of postprandial low iodine numbers, all the data for this investigation were obtained on fasting blood.

Infection: A third feature which may cause the iodine number of the fatty acids of the serum to decrease is infection. This has been demonstrated by Achard and his colleagues,[31] by Stoesser and McQuarrie [32] and by Stoesser.[33] Consequently, it has been conjectured that the low iodine numbers of patients with eczema may be explained on the basis of an inflammatory reaction. It may be pointed out, however, that in this investigation no determinations made while the patient

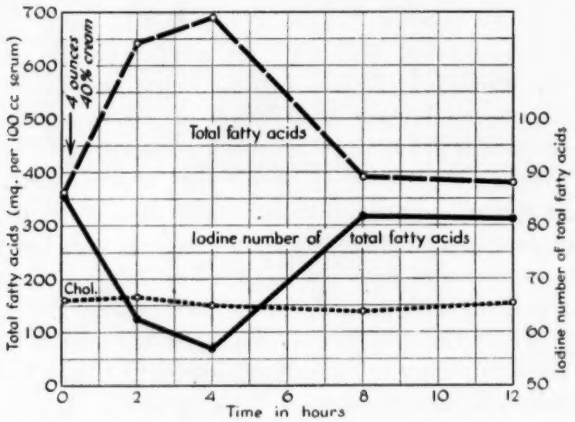

Fig. 9.—Serum lipids following administration of 4 ounces (113.4 Gm.) of 40 per cent cream to patient D. L.

either had fever or signs of respiratory infection have been used in evaluating the relationship between the iodine numbers and eczema.

In an attempt to estimate the influence of inflammation on iodine numbers, some of us [34] have studied the blood lipids of dogs in which

30. Freudenberg, E., and Schornstein, L.: Fettzufuhr und Serumlipoide bei Ekzem und Dermatitis seborrhoides des Säuglings, Ztschr. f. Kinderh. **57**:675, 1936.

31. Achard, C.; Grigaut, A.; Leblanc, A., and David, M.: L'équilibre lipoidique du sérum sanguin dans les maladies aiguës, J. de physiol. et de path. gén. **26**:415 (Sept.) 1928.

32. Stoesser, A. V., and McQuarrie, I.: Influence of Acute Infection and Artificial Fever on Plasma Lipids, Am. J. Dis. Child. **49**:658 (March) 1935.

33. Stoesser, A. V.: Effect of Acute Infection on Iodine Number of Serum Fatty Acids, Proc. Soc. Exper. Biol. & Med. **32**:1326 (May) 1935.

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artificial dermatitis has been produced. The results were only suggestive that a slight decrease in iodine number of the serum lipids accompanied the dermatitis. It must be admitted, however, that the area of the artificially produced dermatitis was small and that the much greater surface usually involved for patients with eczema might have a greater effect on the iodine number of the serum fatty acids. Further attempts to understand these possible relationships have been made by studying the degree of unsaturation of the tissues themselves in the artificially produced dermatitis, and there is some evidence that the iodine number of the tissue lipids was higher when the dermatitis was more extensive. It is not known whether or not there may be a derangement in the lipid metabolism of the tissues in patients with eczema.

In relation to the influence of infection, a point of clinical interest is the fact that eczematous eruptions are almost invariably made worse when infections of the upper respiratory tract are present. We also have observed that an occasional resistant chronic condition of eczema has improved rapidly when the patient was given penicillin intramuscularly. It is possible that a low grade infection was maintaining the eczematoid reaction for these patients.

It may well be that low iodine numbers for the serum lipids in eczema can be explained on the basis of the dermatitis per se, and accompanying infection, type of diet or a combination of such factors, but it does not seem likely that eczema is the direct result of a dietary deficiency in fat. Some of us [34] found that a form of dermatitis could be made by topical application of croton oil dissolved in acetone to the skin of dogs on fat-free or low fat diets, but not in similar animals receiving fresh lard in the diet in place of sucrose, which furnished 28 per cent of the caloric value of the diet low in fat. It would seem probable that the essential fatty acids are required for maintenance of the normal integrity of the skin, but that other factors may be influential in the actual development of the dermatitis.

Significance of Clinical Findings.—The over-all experience of ourselves and others would appear to indicate that the inclusion in the diet of fats rich in unsaturated fatty acids is of definite benefit in a majority of eczematous patients even without other forms of therapy. We wish to emphasize, however, that such dietary regulation does not dispose of the necessity for meticulous investigation of the need for specific local therapy, elimination of irritating factors and special precautions regarding maintenance of an adequate diet for normal nutrition. In our experience the combination of the unsaturated fatty acid regimen with such therapeutic procedures as topical application of crude coal tar ointment and elimination from the diet of all foods to which the patient is known to be sensitive has proved to be most successful.

The use of unsaturated fatty acid containing soy bean preparations as milk substitutes appears to us to be beneficial to a degree greater than would be anticipated on the basis of relief from sensitivity to the milk proteins alone. It has been observed empirically also that sensitivity to wheat gradually may be reduced after the addition of lard to the diet. Prolonged ingestion of unsaturated fats thus appears to render the skin less susceptible to eczematous eruptions of the allergic type. However, our experience has not indicated that such fats have any influence on the allergic reactions of hay fever or asthma, as claimed by some observers.

SUMMARY

Clinical and blood lipid studies were made in 225 patients with eczema and 101 control subjects.

When used as the sole form of therapy in 148 eczematous patients of various ages, addition to the diet of fats rich in unsaturated fatty acids, such as lard and certain vegetable oils, produced a clinical response judged to be good to excellent in 60 and fair to good in 51. The remaining 37 patients showed slight or no benefit. Most of the latter were in the older age group.

Serum lipid studies on 171 of the eczematous patients disclosed that 80 per cent of infants under 2 years of age, 75 per cent of children between 2 and 15 years, inclusive, and slightly over 50 per cent of adults had iodine numbers for the serum fatty acids below the mean values for the 101 control subjects.

Periodic studies of the serum lipids for patients with eczema revealed a tendency for the iodine numbers of the serum fatty acids to increase as the clinical condition improved following supplementation of the diet with fats rich in unsaturated fatty acids. An increase in the degree of unsaturation of the serum fatty acids was observed also to coincide with clinical improvement of patients treated solely with crude coal tar ointment.

The specific role of the essential fatty acids appears to be that of restoring and maintaining normal nutrition of the skin.

The routine inclusion of unsaturated fatty acids in the diet, while known allergens and other irritants of the skin were avoided, was found to afford the best protection against recurrent attacks of eczema, particularly in infants and young children.

ABSTRACT OF DISCUSSION

DR. ALTON GOLDBLOOM, Montreal, Canada: Through long and careful studies, Dr. Hansen and his associates have established that children suffering from eczematous eruptions manifest a lesser degree of unsaturation of serum lipids than do normal infants. The iodine number of serum lipids is low when the eczema is at its worst and high after improvement. It is for us to ponder the causal relationship between this phenomenon and the disease. It is true indeed

that Stoesser has shown that the same phenomenon occurs in infants during acute infections, even when no eczema is present; yet the fact remains that when eczema is at its worst, unsaturated serum lipids are at their lowest. Can this be merely a manifestation of the infection which must perforce accompany any cutaneous lesion in which the surface of the skin is broken, or is it a condition inherent in the eczema itself? This is a question which much further investigation may answer.

Again, if the fact of low concentration of unsaturated serum lipids is accepted, can one argue that the mere administration of unsaturated oils will improve eczema? There is a low serum phosphorus in rickets, but we physicians do not attempt to cure rickets by the administration of phosphorus—not any more, although we did quite unsuccessfully many years ago. We cure rickets by the administration of a substance which regulates calcium and phosphorus metabolism. Can it be that it is so with eczema? Is the derangement of lipid metabolism amenable to correction by some means yet to be demonstrated, rather than by the administration of more of the substance which the organism cannot utilize? Such questions come to mind when one considers this problem. It would seem to me that, if eczema is caused by a reduction in unsaturated serum lipids, it would be cured by the discovery and control of that mechanism in the organism which regulates the metabolism of saturated and unsaturated fats.

The recently revealed properties of the dithiol propanols and trithiopropanols in regulating seriously deranged or damaged enzyme systems would seem to shed light on this perplexing problem, for we are being led to the realization that most, if not all, chemical changes in the body take place through the medium of enzyme systems. If eczema is related to some disturbance in lipid metabolism, then that disturbance probably results from the derangement of an enzyme system, and further investigation should be directed toward the identification of the enzyme system involved.

The work of Peters and his associates at Oxford has shown that if a sulfhydril grouping is involved in the enzyme system, one or other of the series of compounds derived from British Anti-Lewisite (or BAL) will be effective in restoring that enzyme system. If such a grouping is involved in eczema, then BAL or some related compound may provide the answer. If a sulfhydril grouping is not implicated, then time and research may one day provide the answer.

It would appear that the next steps in this research should be directed toward a study of the effects of the thiopropanols on the activity of enzymes in the metabolism of lipids. The effects of the thiopropanols on the activity of enzymes will soon become one of our major preoccupations, and will absorb much of our interest when the full force of Peters' discovery becomes more widely appreciated. I am sure that a study of the relation of these and other substances to the state of lipid unsaturation and their effect on eczema will be productive of much important information and could well be the means of solving this important problem.

DR. ALBERT V. STOESSER, Minneapolis: I am happy to discuss Dr. Hansen's paper, since at the University of Minnesota we are continuing research on the same subject.

Dr. Hansen's experiments on dogs are most interesting, since they reveal that removal of certain fats from the diet leads to changes in the skin. These experiments can be reproduced many times, and it must be remembered that in refeeding the dogs the type of fat will have a great deal to do with the composition of the fat of the animals.

The same disturbances in the diet appear to have an influence on the fat composition of the human being. This observation indicates that making some change in the diet for the treatment of children with infantile eczema is a move in the right direction, especially in view of the fact that their blood fats are often not found to be within the normal range.

There are a few things which should be emphasized in this discussion. They are more practical than scientific. First, the supplements recommended for the diet are not the whole treatment of eczema. A great deal of difficulty has arisen with this idea in our part of the country, and some physicians have come to the conclusion that changes in the diet do not work.

In the cases of eczema, an external treatment, elimination of certain foods in the diet and the administration of substances high in unsaturated fatty acids are all important. Physicians who have given only the various fats may have disappointing results. There are several preparations on the market which have more or less built up the idea that all that is necessary is to feed an eczematous infant substances high in unsaturated fatty acids. This is most misleading.

Of secondary importance is the fact that all children do not have the same level of iodine number of the unsaturated fatty acid of the blood at the time of the first examination. The closer the iodine number is to the normal of 100 the more difficult it is for the infant to respond favorably to the administration of any preparation high in unsaturated fatty acids. There are children who have a low iodine number, down around 60. When they are given preparations of highly unsaturated fatty acids, the iodine number swings upward to the normal and there is a coinciding clinical improvement in the eczema.

Infants which have the low iodine numbers are those which have the so-called true allergic or atopic type of eczema with formation of vesicles and weeping. This eczema, starting in the flushing area of the cheek, may spread over the body. It is more likely to respond to Dr. Hansen's therapy than the type starting in the scalp, with scales and ending up with a generalized dryness of the skin.

In conclusion, it may be stated that the scientific work of Dr. Hansen is a satisfactory therapeutic measure only if children are classified in order that the correct schedule for treatment may be offered. It is practically impossible to carry out the lipid studies on the blood of the patients seen in private practice.

Dr. Arild E. Hansen, Galveston, Tex.: I want to thank Dr. Goldbloom for his well stated and considerate remarks. I am pleased to hear him stress the importance of fundamental investigation regarding such problems. There are two things which I wish to emphasize in regard to the field of the essential fatty acids. The first is that the methods for their determination are extremely inadequate or lacking from a practical viewpoint. The second is that in spite of the tremendous amount of laboratory work which has been done, the exact physiologic and functional role of the essential fatty acids has not been determined.

Dr. Stoesser already has emphasized the point that never have we stated that the administration of unsaturated fatty acids is a substitute for other therapeutic control for infantile eczema. They are an adjunct to be used in addition to good general and local therapy. We believe, however, that the essential fatty acids may be one of the factors which are concerned with the normal functioning of the skin. Certainly a great deal of fundamental work is necessary, and I am hopeful that investigations in this field will be continued.

SUBSTITUTION TRANSFUSION: A NEW TREATMENT FOR SEVERE ERYTHROBLASTOSIS FETALIS

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ERYTHROBLASTOSIS fetalis has long been recognized as a hemolytic disease of unknown origin with varying degrees of anemia and hepatic damage. The historical aspect of the problem has been thoroughly covered by Javert,[1] Potter [2] and others. The forms manifested by the illness were individually described by many writers, and a relationship between fetal hydrops, icterus gravis and congenital hemolytic anemia of the newborn was assumed in 1932.[3] Other unclassified varieties of the syndrome are known to exist.[4]

Therapy, even before the recent elucidation of the pathogenesis, was directed at correction of the anemia by repeated transfusions. This treatment proved effective in some instances, but in the majority of cases there were severe reactions, with increased hemolysis, fever and death. These reactions are now known to have been caused by the use of Rh-positive blood from random donors, and from the fathers, whose erythrocytes always carried the same antigenic factor as the blood of the affected infants.

Since 1941 refinements in the treatment of erythroblastosis, based on the role of the Rh factor,[5] have resulted in a decidedly improved

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2. Potter, E. L.: Present Status of Rh Factor, Am. J. Dis. Child. **68**:32 (July) 1944.

3. Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of Fetus, Icterus Gravis Neonatorum and Anemia of Newborn, J. Pediat. **1**:269 (Sept.) 1932.

4. Wallerstein, H., and Weisman, A. I.: Unpublished data. Javert.[1]

5. (*a*) Landsteiner, K., and Weiner, A. S.: Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223 (Jan.) 1940. (*b*) Levine, P., and Katzin, E. M.: Isoimmunization in Pregnancy and Varieties of Isoagglutinins Observed, ibid. **45**:343 (Oct.) 1940. (*c*) Levine, P.; Burnham, L.; Katzin, E. M., and Vogel, P.: Role of Iso-immunization in Pathogenesis of Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **42**:925 (Dec.) 1941. (*d*) Levine, P.; Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy: Its Possible Bearing on Etiology of Erythroblastosis Foetalis, J. A. M. A. **116**:825 (March 1) 1941.

prognosis.[6] Nevertheless, one variety of the illness, icterus gravis, continues to present a difficult therapeutic problem, with a persistently high mortality rate. The commonest routine followed at present consists of repeated transfusions of Rh-negative blood inaugurated soon after birth [7] or immediately at birth.[8] When it is expected that the baby will have a severe form of the disease, it has been recommended [9] that delivery be induced prematurely in order to reduce the period of exposure to the maternal antibody. Babies who might otherwise have succumbed may have been saved by this method. Others, however, have had increasing jaundice despite the transfusions with Rh-negative blood, and have eventually died with postmortem findings identical to those seen in untreated patients.

Discussing the pathogenesis of erythroblastosis, Davidsohn [10] has emphasized the significance of hepatic damage induced by excessive red blood cell hemolysis and the accompanying reactive liver erythropoiesis. With this physiologic concept of the significant pathologic changes involved, it was clear that a new and radically different approach to the therapy of erythroblastosis was required. Such a method must seek either to remove the end products of hemolysis or to prevent their formation in excessive amounts by the removal of the Rh-positive erythrocytes before they are destroyed in large numbers by the maternal antibody. In this way the progressive hepatic damage might be arrested and the element of toxicity removed.

It has been shown in a preliminary report [11] that a method to carry out this purpose was feasible and practicable. The procedure consists of the actual withdrawal of the infant's Rh-positive cells and their replacement with innocuous Rh-negative erythrocytes. In order to

6. (*a*) Javert, C. T.: Further Studies on Erythroblastosis Neonatorum of Obstetric Significance, Am. J. Obst. & Gynec. **43**:921 (June) 1942. (*b*) Gimson, J. D.: Haemolytic Disease of Newborn (Erythroblastosis Foetalis): Its Treatment with Rhesus-Negative Blood, Brit. M. J. **2**:293 (Sept. 4) 1943.

7. Wiener, A. S., and Wexler, I. B.: Transfusion Therapy of Acute Hemolytic Anemia of Newborn, Am. J. Clin. Path. **13**:393 (Aug.) 1943.

8. Mayes, H. W.: Cord Transfusions in Newborn Infants: Report of Ninety-Nine Cord Transfusions in Premature Babies, Twenty-One in Full Term Babies and Seventy-Eight in Babies of Rh Negative Mothers, J. Pediat. **28**:69 (Jan.) 1946. Harville, C. H.: Cord Transfusion in Management of Prematurely Delivered Infant with Erythroblastosis Fetalis, J. A. M. A. **129**:801 (Nov. 17) 1945.

9. Buxton, B. H., and McDuff, H. C.: Erythroblastosis Fetalis, Rhode Island M. J. **28**:333 (May) 1945.

10. Davidsohn, I.: Fetal Erythroblastosis, J. A. M. A. **127**:533 (March 17) 1945.

11. Wallerstein, H.: Treatment of Severe Erythroblastosis by Simultaneous Removal and Replacement of the Blood of the Newborn Infant, Science **103**:583 (May 10) 1946.

avoid subjecting the child to the dangers of shock from exsanguination, the withdrawal and replacement are carried out simultaneously.

It can be shown mathematically that if a continuous transfusion and withdrawal are carried out for sixty minutes, if the mixing is considered the equivalent of instantaneous, and if the baby's blood volume is approximately 250 cc., only 36.7 per cent of the original blood will remain. To test this calculation, my colleagues and I duplicated the conditions by the use of an aspirator bottle containing 250 cc. of tenth normal hydrochloric acid with a pipet for the constant admission of distilled water. The rate of admission was kept equal to the rate of loss of the hydrochloric acid from the aspirator bottle into a measuring cylinder. A stirrer was kept within the aspirator bottle. When 250 cc. of fluid was collected in the cylinder, a sample of the liquid remaining in the aspirator bottle was titrated and showed 0.0367 normal hydrochloric acid.

A variation of the continuous procedure, whereby 50 cc. of blood is removed from the baby and then an equivalent amount administered in alternation, through five exchanges, can be shown arithmetically to permit of an exchange that leaves behind 80 cc. of the original 250 cc. Inasmuch as the infant is given about 100 cc. of Rh-negative blood over and above what is withdrawn, the dilution factor permits a reduction of the original Rh-positive blood to about 25 per cent of the starting volume. The differential typing of the cells removed at the beginning and at the end of the exchange confirms the fact that only 20 to 25 per cent of the original Rh-positive erythrocytes remain. The hemolysis of these cells by the remaining maternal antibody is retarded, and the liver is then not called on to cope with inordinately large amounts of the products of red cell destruction.

TECHNIC

1. The infant is immobilized, with one arm fixed to a board.

2. A superficial vein of the arm is exposed, a cannula inserted, and an infusion of isotonic solution of sodium chloride or pooled plasma, preferably the latter, given by gravity.

3. A ¼ inch (0.64 cm.) 19 gage needle is inserted into the longitudinal sinus through the anterior fontanelle, and withdrawal is performed by syringe.

4. Every specimen removed is placed in a numbered test tube and saved for subsequent determinations of the icterus index and differential agglutination.

5. After about 50 to 60 cc. of blood have been removed from the fontanelle, Rh-negative blood of the same group is permitted to replace the plasma or saline infusion.

6. When an estimated substitution of about 80 per cent has been accomplished, the needle is removed from the fontanelle. The estimate is based on the infant's weight, figuring the total blood volume as about 10 per cent.

7. The infusion is continued until about 75 to 100 cc. of Rh-negative blood is administered in excess of the amount removed.

8. During the procedure, 10 cc. of 10 per cent calcium gluconate is injected by syringe through the cannula in the vein, to counteract the large amount of citrate in the blood or plasma.[12]

9. The procedure takes from one-half to one and one-half hours, depending on the size of the baby, the amount of blood substituted and the ease with which bleeding can be completed.

For those who object to the use of the fontanelle, there are other sites for the bleeding. It is usually difficult to obtain sufficient blood from the superficial veins. One case has recently been called to my attention in which the operator was able to bleed the baby from the free end of a cut vein while the infusion was given in the opposite direction in the same vein. In a recent case, I have followed the suggestion of Dr. S. H. Polayes[13] and used the radial artery for exsanguination. The infusion was set up in the usual manner by cannulizing the medan cephalic vein. A second incision was made at the wrist and a small branch of the radial artery exposed at that point. A cannula was inserted and the artery permitted to bleed. With this altered technic it was found possible to regulate the ingress and egress of blood so that a continuous and thorough replacement of the blood volume could be accomplished. The radial artery is chosen at this location because the superficial and deep volar arches offer an ideal natural anastomosis. There appears to be little risk involved, since the anastomoses both above and below the site of cannulization of the artery are adequate, and anomalies of the artery in this area are known to be rare. It must be remembered that in the newborn infant this vessel is small, and bleeding may still be somewhat more difficult than anticipated. Recently Dr. P. Vogel[14] overcame this handicap by heparinizing the baby and thereby obtaining a free flow of blood.[15]

The results obtained with the replacement technic are illustrated by the following cases:

REPORT OF CASES

CASE 1.—Mrs. D. gave birth to a normal first child. Her second baby, a boy, was delivered spontaneously at forty weeks' gestation by Dr. M. Brandt at the Jewish Memorial Hospital. The infant weighed 6 pounds and 13 ounces (3,090 Gm.) and was apparently normal. Within twenty-four hours severe jaundice developed, and he was rather toxic and listless. The hemoglobin content was 17.5 Gm. per hundred cubic centimeters; there were 4,650,000 erythrocytes and

12. Sherman, I.; Alperstein, B. B., and Sherman, B.: Intravenous Calcium Gluconate as an Aid in Reduction of Post-Transfusion Reactions, New York State J. Med. **43**:2419 (Dec. 15) 1943.

13. Polayes, S. H.: Personal communication to the author.

14. Vogel, P.: Personal communication to the author.

15. Blocking antibodies were found in the serum of the mother and of the infant. Two hundred and twenty cubic centimeters of the baby's blood was replaced with 320 cc. of Rh-negative blood. The patient subsequently made an uneventful recovery.

20,000 erythroblasts (43 per 10,000 red blood cells). The blood group was O, Rh positive, and the mother's blood was Rh negative with anti-Rh agglutinins present.

Forty cubic centimeters of the baby's blood was removed and replaced with 125 cc. of Rh-negative blood. Twenty-four hours later there was no change in the hematologic picture, but the clinical appearance was worse. The jaundice had deepened, the liver and spleen were now palpable, and feedings were taken poorly. The substitution was repeated, another 40 cc. being replaced with 125 cc. of Rh-negative blood. In another twenty-four hours the infant appeared brighter and was taking feedings well. The jaundice now regressed rapidly, and the baby was discharged on the ninth day, with 16.5 Gm. of hemoglobin and 4,700,000 erythrocytes. Three months later the child was well, progressing normally, and without evidence of anemia or other sequelae.

CASE 2.—Mrs. W., a patient of Dr. Brandt's Obstetric Service at the Jewish Memorial Hospital, had an extremely bad previous history. Three children were alive and well, 1 having required transfusion therapy. There were 2 miscarriages, 5 stillbirths, and 1 baby who died immediately after birth, with postmortem findings of erythroblastosis. One week before delivery the anti-Rh agglutinin titer was 1 : 1,024.

She was admitted to the hospital and delivered of a boy by cesarian section at thirty-eight weeks' gestation. The baby weighed 4 pounds and 7 ounces (2,013 Gm.). The blood group was O, Rh positive. The hemoglobin content was 14.5 Gm. per hundred cubic centimeters, and the red cell count 3,900,000 with 30,000 erythroblasts (77 per 10,000 red blood cells). When the baby was 27 minutes old, 165 cc. of blood was removed and replaced with 225 cc. of Rh-negative blood. The procedure was completed in thirty-seven minutes, and the infant showed no signs of distress. It is significant that when the bleeding was begun and the arm vein exposed the infant did not cry. At the end of the transfusion he cried with vigor and was obviously more responsive. In twenty-four hours there was mild jaundice and the spleen was palpable. The baby was active, with good muscle tonus, and took its feedings well. In seventy-two hours the jaundice faded and the infant showed a gain in weight. He was discharged on the sixteenth day with 14.5 Gm. of hemoglobin and 4,260,000 erythrocytes.

Five weeks later the baby had gained 1½ pounds (680 Gm.). However, there was a definite anemia, with only 7.5 Gm. of hemoglobin. There were no Rh-positive cells in the circulation. An ordinary transfusion of 75 cc. of Rh-negative blood was given intratibially, although at this time Rh-positive blood would have sufficed. The baby was discharged twenty-four hours later and has improved steadily since. Ten months later the child was normal in every respect.

CASE 3.—Mrs. C had previously given birth to a normal baby. Her second, a girl, was delivered spontaneously at term by Dr. L. J. Hershkowitz at the Kew Gardens General Hospital. The infant weighed 7 pounds and 8 ounces (3,402 Gm.) and was apparently normal. When first seen by me she was 56 hours old, intensely jaundiced and hyperirritable, with a shrill cry when handled. The spleen was considerably enlarged. The hemoglobin content was 13 Gm.; there were 3,940,000 erythrocytes and 26,000 erythroblasts (66 per 10,000 red blood cells). The icterus index was 625. The blood group was O, Rh positive. The mother's blood was Rh negative with an anti-Rh titer of 1 : 65,536.

A substitution transfusion was performed. Two hundred and twenty-five cubic centimeters of the baby's blood was removed and replaced with 300 cc. of Rh-negative blood. This was followed by a gain in weight and absence of further

toxicity. Three days later, however, streaks of blood were noted on the diaper. A simple transfusion of 75 cc. of Rh-negative blood was given intratibially, and vitamin K was also given. The infant continued to improve and was discharged three weeks later in good condition. Six months later the hemoglobin content was 16.5 Gm. The general condition appeared excellent, but the child is still being observed for possible sequelae in the nervous system.

CASE 4.—Mrs. D. had previously given birth to 2 normal babies. Her third was a boy, delivered spontaneously at full term by Dr. Flemming's Obstetric Service at the Queens General Hospital. The infant weighed 7 pounds and ½ ounce (3,189.3 Gm.) and was apparently normal at birth. In twenty-four hours jaundice appeared. The hemoglobin content was 14 Gm., and the red blood cells 3,860,000. The blood group was O, Rh positive. The mother's blood was Rh negative with anti-Rh agglutinins in a concentration of 1:16. The baby was given a transfusion of 50 cc. of blood which was subsequently found to be Rh positive. When first seen by me the baby was 72 hours old. He was intensely jaundiced and markedly spastic. The spleen and the liver were enlarged and firm. Feedings were taken poorly and were regurgitated.

Two hundred and seventy-five cubic centimeters of the baby's blood was removed and replaced with 350 cc. of Rh-negative blood. The clinical picture improved immediately, although there was some residual anemia for one month. The jaundice regressed in a few days, and the child gained weight and was discharged with no further therapy.

CASE 5.—Baby S., first-born boy, was delivered spontaneously at term by the Obstetric Service of the Jewish Memorial Hospital. He weighed 7 pounds and 2 ounces (3,232 Gm.). Within twelve hours there were jaundice, cutaneous petechiae, purpuric spots and bloody stools. The baby was apathetic, and feedings were taken poorly. The infant was Rh positive and the mother Rh negative with no demonstrable antibodies. There was only moderate anemia. Sixty cubic centimeters of the baby's blood was replaced with 75 cc. of Rh-negative blood and 100 cc. of pooled plasma. Vitamin K was also given. The hemorrhagic tendency was immediately arrested, and recovery was prompt. Six months later there were no signs of anemia or other sequelae.

CASE 6.—Mrs. N. had given birth to a normal first child. Her second, a girl, was delivered spontaneously at full term by Dr. Flemming's Obstetric Service at the Queens General Hospital. The infant weighed 6 pounds 14 ounces (3,118 Gm.) and was apparently normal. In a few hours jaundice became apparent, and in twenty-four hours the icterus index was 52. The hemoglobin was 12 Gm., the erythrocyte count was 3,950,000, and many nucleated red cells were seen on the stained smear. Twenty-four hours later the red count had dropped to 3,150,000. The infant was deeply jaundiced and lethargic, and did not take its feedings well.

When first seen by me, the baby was 48 hours old. The blood group was A, Rh positive. The mother's blood group was O, Rh positive, and her serum contained anti-A agglutinins in a titer of 1:1,024 and anti-B in a titer of 1:32. One hundred and eighty cubic centimeters of the baby's blood was removed and replaced with 280 cc. of O, Rh-negative erythrocytes resuspended in pooled plasma. Twenty-four hours later the hemoglobin content was 15 Gm. and the red cell count was 5,950,000. No nucleated red cells were seen. The patient was discharged on the thirteenth day with an erythrocyte count of 5,200,000 and an icterus index of 5.

CASE 7.—Mrs. L. had been pregnant four times previously. The first baby, a boy, was now 9 years old and had shown no evidence of erythroblastosis. The

next three pregnancies had resulted in two early abortions (second month) and one stillbirth, at six months. During her fifth pregnancy she was tested serologically and found to be Rh negative with blocking antibodies which became strong in the eighth month. The husband and first child were Rh positive. Medical induction of labor was recommended, but proved ineffectual. She was delivered at term, after a prolonged labor, by Dr. A. Tamis at the Jewish Memorial Hospital; the infant was a boy and weighed 8 pounds (3,628.7 Gm.).

At birth the baby required artificial resuscitation, possibly because of sedatives given to the mother during labor. The hemoglobin content was 23.5 Gm., the red count 6,260,000, and there were 31,000 erythroblasts (50 per 10,000 red blood cells). The blood group was A, Rh positive. The icterus index was 34. The total protein was 4.3 Gm. per hundred cubic centimeters. The baby was cyanotic, and there was moderate generalized edema. The spleen was palpable. The cry was weak.

When the baby was ten hours old, 375 cc. of blood was removed and replaced with 450 cc. of A, Rh negative blood. In twenty-four hours the hemoglobin content was 17.5 Gm. The jaundice was slight and regressed rapidly. There was no evidence of edema. The infant was discharged on the eighth day with a hemoglobin content of 17 Gm.

In all 7 cases the prognosis was exceedingly grave. In all but the second and the seventh case the infants were first seen by pediatricians, who, in each instance, gave a poor prognosis. In case 2 the previous maternal history was so bad as to make it relatively easy to gain permission for what was at that time believed to be a radical procedure. In the other cases we were permitted to perform the substitution only because the pediatricians and family physicians agreed that the outlook for recovery was poor. The indication, as voiced by one pediatrician, was "There is nothing to be lost." In cases 3, 4 and 6 there were no evidences of permanent sequelae at the time of the last examination, although the infants were treated late, after kernicterus could have developed. This complication appears in about 10 per cent of erythroblastotic babies[16] and may appear within twenty-four hours after the onset of icterus.[17] It is apparently possible to institute therapy late in the course of the illness and still avoid complications. Best results are to be expected, however, when the procedure is carried out as soon as the baby is born, as in case 2. The dangers of damage to the liver and the brain are then reduced, and the chances for recovery are thus greatly enhanced.

In the first case, the technic for bleeding had not yet been developed. We were unable to remove more than 40 cc. of blood at each attempt. Whether or not this baby would have recovered with simple trans-

16. McIntosh, R.: Jaundice as Pediatrician Sees It, Canad. M. A. J. **45**:488 (Dec.) 1941. Yannet, H., and Lieberman, R.: Rh Factor in Etiology of Mental Deficiency, Am. J. Ment. Deficiency **49**:133 (Oct.) 1944.

17. Fitzgerald, G. M.; Greenfield, J. G., and Kounine, B.: Neurological Sequelae of "Kernicterus," Brain **62**:292 (Sept.) 1939.

fusions is open to question. The infant was rather toxic and listless before treatment was instituted and was so much improved after the second bleeding that it is probable that the comparatively small reduction in Rh-positive cells was sufficient to limit the hemolysis to the point where no permanent damaging effects were sustained. Wiener and his associates [18] reported a similar attempt at exsanguination with equal difficulties in bleeding. A partial withdrawal of 50 cc. was performed, but the infant died on the fifth day. The same workers subsequently succeeded in carrying out the exchange experimentally on a mongolian idiot.

In the remaining 6 cases the procedure was carried out smoothly and with no difficulty. The importance of early institution of treatment bears repetition. The method of transfusion here described is not a palliative or supportive measure. It is designed to act as a prophylaxis against the effects of severe destruction of blood. As with all prophylactic methods, it must be performed before the illness is completely manifest; otherwise the preventive element is impaired or completely lost. Some babies will recover even if treated late. This is probably due to the removal of the toxic end products of blood destruction rather than to the prevention of that hemolysis. In a few of this group permanent changes may develop in the liver or the nervous system. Others with intense jaundice may not benefit at all from this or any other method when the hemolysis has progressed for a comparatively long time. This is exemplified by the following cases:

CASE 8.—Mrs. R. had previously given birth to 1 normal baby. Fourteen years later her second baby, a boy, was delivered spontaneously at term by Dr. A. Tamis at the Royal Hospital. Jaundice appeared in twenty-four hours. The hemoglobin content was 14 Gm. and the erythrocyte count 4,100,000, with 22,000 erythroblasts (55 per 10,000 red blood cells). The baby was Rh positive and the mother Rh negative with a weak blocking antibody. Treatment was instituted when the child was 60 hours old. At that time the icterus index was 260, the alkaline phosphatase 12 units, the serum albumin 3 Gm. and the serum globulin 2.3 Gm. The cephalin flocculation test elicited a strongly positive reaction. The baby's condition was poor, and it was necessary to give stimulation before the transfusion was performed. One hundred and twenty-five cubic centimeters of blood was removed and replaced with 225 cc. of Rh negative blood. Administration of oxygen and stimulation were continued throughout the night but the infant died in about twelve hours.

At autopsy all the typical evidences of erythroblastosis were seen, with splenomegaly, hepatomegaly and pronounced staining of the basal nuclei with bile.

CASE 9.—Mrs. P. had previously borne 3 children who showed no evidence of illness. Fourteen months after the birth of her third child she was delivered spon-

18. Wiener, A. S.; Wexler, I. B., and Gamrin, E.: Hemolytic Disease of Fetus and Newborn Infant with Special Reference to Transfusion Therapy and Use of Biologic Test for Detecting Rh Sensitivity, Am. J. Dis. Child. **68**:317 (Nov.) 1944.

taneously of a girl at full term by Dr. N. Solomon at the Royal Hospital. The baby appeared normal at birth, but in twenty-four hours jaundice developed which increased considerably during the next twenty-four hours. The hemoglobin content was 8.5 Gm. and the red blood cell count 2,970,000, with 49,000 erythroblasts (165 per 10,000 red blood cells). The blood group was A, Rh positive, and the mother's blood was Rh negative with blocking antibody in the lower dilutions. The icterus index was 144, the alkaline phosphatase 30 units, the reaction to the cephalin flocculation test strongly positive, and the albumin-globulin ratio reversed. Before the substitution transfusion was performed the child was given oxygen and stimulants. This was continued throughout the procedure. Two hundred cubic centimeters of the baby's blood was removed via the radial artery and replaced with 300 cc. of Rh-negative blood. Death occurred two hours later.

The autopsy revealed all the typical evidences of erythroblastosis with pronounced kernicterus. The radial artery was studied and showed no thrombus.

It is my opinion that both these babies might have recovered if treatment could have been instituted during the first twenty-four hours of life.

COMMENT

Erythroblastosis fetalis occurs in approximately 1 of every 200 births. There are at least three manifestations of the disease—congenital hemolytic anemia, fetal hydrops and icterus gravis. The last-named type is the most difficult to diagnose early and is the one in which proper therapy holds out the most promise. The mortality rate in this variety is high. Reported statistics on mortality rates vary, depending on whether or not the writer included in his series all the forms of the illness. This variation is exemplified by the reports of Javert, who, in one series of 55 cases [1] which included fetal hydrops, icterus gravis, congenital anemia and 3 unclassified fatal cases, had a mortality rate of 70 per cent. The same author [6a] in a later smaller series which included no cases of fetal hydrops found only 17 per cent mortality. Such comparisons have been mistakenly interpreted as indicating a vastly improved prognosis in all forms of the disease. Prior to the development of the present treatment, and only in cases of icterus gravis in which treatment was given, I have experienced a mortality rate of about 35 per cent. The significance of this fact is enhanced by the circumstance that icterus gravis constitutes the commonest form of the erythroblastosis syndrome.[2]

Up to the present time the routine treatment of erythroblastosis has consisted of repeated transfusions of Rh-negative blood initiated early in the disease. In cases in which there is a previous history of fetal or neonatal morbidity or mortality from this cause, premature delivery is often recommended,[9] to be followed by transfusion immediately after birth. The early delivery constitutes a form of prophylactic therapy. Transfusions are given many of these infants at a time when they show no evidence of illness. The hope is that with this routine the progressive anemia is checked, the oxgen-carrying capacity maintained, and the hepatic function bolstered by the infused blood proteins.

The value of premature delivery is open to question. At what point the hazard of prematurity is less than the hazard of continuing the exposure to the maternal antibody is as yet undetermined. It is conceded by most investigators that prematurity in erythroblastosis is a bad complicating factor. It is also known that most of the infants are born with little or no sign of illness, suggesting that some protective mechanism may function during intrauterine life. Javert [1] expressed the opinion that before birth the increased bilirubin may pass into the maternal circulation and elevate the mother's icterus index. Levine [19] suggested that the maternal antibody may be stored in the fetal tissues and that the release of this antibody in the neonatal period constitutes the greatest danger to the infant. On the other hand, there is a tendency toward premature labor in these mothers,[20] and the infants often do show severe anemia or jaundice at birth. The occurrence of fetal hydrops also indicates that protective mechanisms are not always operative. It would therefore seem reasonable that in certain selected instances (as in cases 2 and 7) when the mother's history and antibody studies so warrant, and viability has been reached, careful attention be paid to the fetus and pregnancy be interrupted at the first signs of distress. The technic selected for the interruption of pregnancy should be one that is least threatening to the health of the mother.

While this plan of induced labor or cesarian section with immediate transfusion has succeeded in saving many infants, many others so treated do nevertheless have progressive icterus, with pronounced hepatomegaly and splenomegaly despite little or no anemia, followed by severe toxicity and death, often in two to three days. The prognosis is often worse in infants who present little or no anemia at birth, but in whom a rapidly intensifying jaundice develops.

Such experiences have been reported time and again, and continue to occur even though the amount of blood transfused in the multiple procedures has often exceeded the total original blood volume of the baby. During this period all or nearly all of the infant's Rh-positive blood is destroyed,[21] and the blood may become temporarily Rh negative [22] because the transfused red blood cells are the only ones remaining in the circulation. In some of these babies the liver is unable to cope with the large quantities of bilirubin and toxic products thus liberated.

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19. Levine, P.: Pathogenesis of Erythroblastosis Fetalis: Review, J. Pediat. **23**:656 (Dec.) 1943; correction, ibid. **24**:221 (Feb.) 1944.

20. Potter.[2] Buxton and McDuff.[9]

21. Brown, H. R., and Levine, P.: Rh Factor and Its Importance in Transfusion for Anemias of Erythroblastosis and Other Causes. Case Reports, J. Pediat. **23**:290 (Sept.) 1943.

22. Mollison, P. L.: Survival of Transfused Erythrocytes in Hemolytic Disease of Newborn, Arch. Dis. Childhood **18**:161 (Dec.) 1943.

Failure of therapy lies in the mistaken emphasis on the anemia as the most important indication for treatment. A consideration of the role of the liver and other susceptible tissues in the pathogenesis of erythroblastosis leads to a different viewpoint as to the more significant pathologic changes and the most efficient form of therapy.

Davidsohn [10] has hypothesized that with the development of isohemolysis three integrated pathologic changes occur to damage the hepatic cell. These are: (1) anoxemia and endothelial damage, (2) extramedullary erythropoiesis with pressure atrophy and circulatory impairment and (3) intrahepatic biliary stasis resulting in obstructive jaundice. These mechanisms then perpetuate themselves in a vicious cycle which continues until the more pronounced manifestations of hepatic disease, such as severe icterus, anemia, purpura and hypoproteinemia with edema, become evident. As a result, the hepatic cell itself undergoes degeneration, producing a hepatocellular jaundice and hypoproteinemia. The importance of these changes in the liver has also been stressed by other writers, and Potter [2] has stated that the chances for recovery depend on the extent to which the liver is involved.

We have recently tried to correlate the changes in the liver in the living patient by studying the blood chemistry in 5 cases. In addition to a high icterus index, we have found a low total protein content with reversal of the albumin-globulin ratio, a high alkaline phosphatase content and positive reactions to cephalin flocculation tests. Similar observations concerning the chemistry of the blood have been previously made.[1] More definite conclusions from such studies may be forthcoming when a larger series is collected.

It should be obvious that if therapy is to be successful in more of these infants, the morphologic and physiologic changes which have been shown to occur and to progress during and despite treatment by repeated transfusions must be prevented. To this end, Darrow [23] advocated transfusions of Rh-positive blood. She suggested that adding Rh-positive cells to the circulation would spare the baby's cells by neutralizing the maternal antibody. This is, in effect, a return to the therapy used before the discovery of the Rh factor, when repeated transfusions from random donors also resulted in occasional success. Some infants are known to recover spontaneously, and it is probable that those who appear to benefit from Rh-positive blood would do as well without therapy. It has been suggested [24] that if no other blood is available for transfusion, Rh-positive blood may be used, but only as a temporary expedient

23. Darrow, R. R.: Treatment of Erythroblastosis Fetalis, J. A. M. A. **127:** 1146 (April 28) 1945.

24. Potter.[2] Brandes, E. B., and Cushman, H. R.: Erythroblastosis Fetalis: Case Report, J. Pediat. **25:**239 (Sept.) 1944. Wiener, A. S.: Rh Blood Types and Some of Their Applications, Am. J. Clin. Path. **15:**106 (March) 1945.

to combat anoxemia and only until Rh-negative blood can be obtained. When considering the use of Rh-positive blood it is wise to remember that these cells may not survive for more than two to three days and that severe reactions with increased morbidity may result. Some benefit may, however, be derived from the use of such blood intramuscularly, if the susceptible cells and their products remain out of circulation. With this in mind, we have on occasion used the father's blood intramuscularly as a supplement to other therapy. As yet it has not been possible to evaluate the merit of this procedure.

If one accepts the protection of the liver as the primary indication for therapy, one must also assume that permitting the infant's erythrocytes to be completely destroyed may prove too great a burden for hepatic function. Maintaining the circulation and the oxygen-carrying capacity of the blood with repeated transfusions, even of Rh-negative blood, is thus often insufficient. It is important to prevent this massive hemolysis of erythrocytes. This can be accomplished only by the removal of the Rh-positive cells. The method of therapy herein presented not only curtails the hemolytic process but also rapidly substitutes Rh-negative for the Rh-positive blood, without the perils of shock attendant on the separate performance of bleeding and replacement. It can be shown by differential agglutination tests that 80 per cent or more of the Rh-positive cells can be removed in this fashion. Where impairment of hepatic function and kernicterus are likely to prove the predominating changes, such a method becomes a life-saving procedure.

Only about 30 per cent of erythroblastotic babies born alive incur severe hepatic damage, and only about 10 per cent show kernicterus. Until such time as familiarity with the procedure and the development of skill in the performance of the substitution transfusion become more widespread, the use of the method must be limited to those cases in which it is most apt to be required. In time, unless more accurate criteria for the selection of cases are developed, it may prove worth while to use this routine as a prophylactic in all cases in which there has been a previous history of erythroblastosis.

Since it is true that the greatest benefits from this form of therapy are derived when it is practiced in the period immediately after birth, it is often necessary to decide on the procedure before delivery takes place. In the selection of these cases, the following criteria, established during pregnancy, will prove of value.

1. *History of Previous Erythroblastotic Babies.*—Multiparity is an important predisposing factor. In one series[19] 91 per cent of the affected infants were offspring of multiparous women. Potter[2] confirmed the fact that the illness is ten times as frequent in offspring of multiparous as of primiparous women. Only 1 of the infants reported

on here is a first baby. I believe that this is the most significant single fact in predetermining the fate of the current pregnancy. Unless the father is heterozygous, once erythroblastosis has appeared in a previous pregnancy one may expect that subsequent babies will show increasingly severe forms of the disease.

2. *Serologic Studies.*—Approximately 92 per cent of the babies with erythroblastosis are born from Rh-negative mothers and Rh-positive fathers. Only about 1 in 25 of such matings, however, results in demonstrable illness in the offspring. The remaining 8 to 10 per cent of the cases result from immunization against the A or B isoagglutinogens,[25] against the Hr factor[26] or against subgroups of the Rh factor.[27] Other atypical agglutinins, some as yet undifferentiated, may also act as causative agents of this syndrome.[28] The mere demonstration of typing differences is not in itself sufficient indication of impending erythroblastosis. It is especially important to demonstrate antibodies in the mother's serum.[29] The theory that univalent (blocking) antibodies are more indicative of severe disease in the fetus[30] has not always been substantiated in my experience. I have thus far encountered 3 cases of blocking antibody in the mother with only mild evidence of hemolytic disease in the infants. Neither does the presence of agglutinins always indicate erythroblastosis in the newborn child.[31] We have encountered like instances. The presence of these antibodies

25. Polayes, S. H.: Erythroblastosis Fetalis in Mothers with Rh Positive Blood: Report of Six Cases with Comment on Isoimmunization with "A" and "B" Agglutinogens, Am. J. Dis. Child. **69**:99 (Feb.) 1945.

26. Levine, P.: On Hr Factor and Rh Genetic Theory, Science **102**:1 (July 6) 1945.

27. Wiener, A. S.: Role of Subtypes in Hemolytic Transfusion Reactions and in Erythroblastosis, Am. J. Clin. Path. **14**:52 (Jan.) 1944.

28. McIvor, B. C., and Lucia, S. P.: Irregular Agglutinin and Erythroblastosis Fetalis (Hemolytic Disease of Newborn), Proc. Soc. Exper. Biol. & Med. **55**:99 (Feb.) 1944. McCall, A. J.; Race, R. R., and Taylor, G. L.: Rhesus Antibody in Rh-Positive Mother Causing Hemolytic Disease of Newborn, Lancet **1**:214 (Feb. 12) 1944.

29. Levine and Katzin.[5b] Gimson.[6b] Race, R. R.; Taylor, G. L.; Cappell, D. F., and McFarlane, M. N.: Rh Factor and Erythroblastosis Fetalis: Investigation of Fifty Families, Brit. M. J. **2**:289 (Sept. 4) 1943. Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: Incidence of Hemolytic Disease of Fetus (Erythroblastosis Fetalis) in Different Families: Value of Serological Tests in Diagnosis and Prognosis, J. Obst. & Gynaec. Brit. Emp. **51**:1 (Feb.) 1944.

30. Wiener, A. S.: New Test (Blocking Test) for Rh Sensitization, Proc. Soc. Exper. Biol. & Med. **56**:173 (June) 1944.

31. Dockeray, G. C., and Sachs, H.: Rh Antibodies in Maternal Circulation Without Clinical Manifestations of Erythroblastosis in the Child, J. Immunol. **48**:241 (April) 1944. Goldbloom, A., and Lubinski, H.: Anti-Rh Agglutinins in the Maternal Blood Without Symptoms of Hemolytic Disease in the Newborn Infant, J. Pediat. **28**:83 (Jan.) 1946.

in increasing titer in repeated tests may be of more significance. Up to the present time the correlation of the mother's previous obstetric history with the serologic studies provides the most important criteria on which to base a prognosis for the expected infant.

Other relevant facts, though of less significance according to present knowledge, include: (1) a history of repeated stillbirths or miscarriages in the latter half of pregnancy,[32] (2) a history of transfusion of the mother with Rh-positive blood,[33] (3) increase in maternal icterus index and uric acid,[1] (4) demonstration of edema of the fetal scalp[34] or a Buddha-like attitude of the fetus by roentgenographic study[1] and (5) excessive enlargement of the uterus.[1]

During delivery or immediately thereafter the following signs may suggest the possibility of erythroblastosis and may act as an indication for early therapy: (1) icteric amniotic fluid, (2) excessively large pale placenta and (3) increased numbers of nucleated red blood cells in the cord blood. Casey and Crowson[35] believe that the presence of 5 or more erythroblasts per 10,000 erythrocytes indicates a poor prognosis even in the absence of Rh incompatibility. In my series this has not been true, and recoveries have occurred with an erythroblast count as high as 75 per 10,000 red blood cells. A high nucleated red cell count or numerous more immature erythroblasts may, however, be of value as an indication for prompt treatment.

Immediate treatment of the baby requires that all therapeutic measures be prepared far in advance. If, on the basis of the foregoing criteria, one anticipates that severe erythroblastosis may develop, it is best that the substitution transfusion be performed as soon as the baby is born, even though there be no definite evidence of disease at the time. There should be available the proper personnel for the procedure, the proper equipment and a supply of Rh-negative blood of all types. If all types are not available one may use Rh-negative O blood universalized by the addition of Witebsky substances,[36] or O cells

32. Levine, P.: Serological Factors as Possible Causes in Spontaneous Abortions, J. Hered. **34**:71 (March) 1943. Cohn, T. D., and Cole, S. L.: Fetal Erythroblastosis and Habitual Abortion, Am. J. Dis. Child. **68**:28 (July) 1944. Hunt, A. B.: Rh Factor in Repeated Abortion and Miscarriage, Proc. Staff Meet., Mayo Clin. **20**:26 (Jan. 24) 1945.

33. Buxton and McDuff.[9] Levine, P., and Waller, R. K.: Erythroblastosis Fetalis in the First-Born, Blood **1**:143 (March) 1946.

34. Hellman, L. M., and Irving, F. C.: X-Ray Diagnosis of Erythroblastosis, Surg., Gynec. & Obst. **67**:296 (Sept.) 1938.

35. Casey, A. E., and Crowson, S. H.: Nucleated Erythrocytes in Newly-Born Infants in Relation to Maternal Rh Compatibility, Proc. Soc. Exper. Biol. & Med. **54**:320 (Dec.) 1943.

36. Witebsky, E.; Klenshoj, N., and Swanson, P.: Preparation and Transfusion of Safe Universal Blood, J. A. M. A. **116**:2654 (June 14) 1941.

washed in saline solution and resuspended in pooled plasma. If no Rh-negative blood is at hand, one may use the mother's cells, thoroughly washed to eliminate the antibody and resuspended in pooled plasma.[37] Plasma must be used as the vehicle because with exsanguination the baby's protein supply is depleted.

It is not unusual in erythroblastosis, even with ordinary transfusions, to find anemia a month or more after the patient's discharge from the hospital. This may also occur following the substitution transfusion. An additional transfusion of 75 to 100 cc. may then be required. At this time Rh-positive blood will suffice.

It is advisable that breast feedings be omitted. The anti-Rh agglutinins may pass into the mother's milk,[38] and if absorbed unchanged from the intestinal tract may subsequently add to the hemolysis.

SUMMARY AND CONCLUSION

A new method of treatment of erythroblastosis fetalis is here presented and discussed.

Substitution transfusion is recommended chiefly as a prophylactic measure. Applied during the subicteric period immediately after birth, the method prevents subsequent damage of the liver and the brain.

When used after the toxic manifestations have become pronounced, the benefits of the procedure may be minimized. Although some of the icteric babies may respond to any form of treatment, it must be remembered that 10 per cent subsequently show mental deficiency and spastic paraplegia.

Attempts to correlate antibody reactions, either quantitatively or qualitatively, with the severity of the illness have not been entirely successful.

The history of erythroblastosis fetalis in a previous infant is emphasized as the important indication for prophylactic treatment, due consideration being given to the serologic and genetic data.

37. Wiener and Wexler.[7] Levine, P.: Pathogenesis of Fetal Erythroblastosis, New York State J. Med. **42**:1928 (Oct. 15) 1942.

38. Witebsky, E.; Anderson, G. W., and Heide, A.: Demonstration of Rh Antibody in Breast Milk, Proc. Soc. Exper. Biol. & Med. **49**:179 (Feb.) 1942.

CHRONIC EOSINOPHILIA

Report of a Case with Necrosis of the Liver, Pulmonary Infiltrations, Anemia and Ascaris Infestation

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WITHIN recent years three "syndromes" centering around eosinophilia and pulmonary changes have been described in the literature; namely, Loeffler's syndrome,[1] tropical eosinophilia or "esinophilic lung"[2] and pulmonary acariasis.[3]

Since the description of these syndromes many cases of eosinophilic leukocytosis with pulmonary changes have been reported. Most of these cases have been found to occur in foreign countries, and only a relatively few in this country. It is primarily for this reason that the following case of eosinophilia with pulmonary infiltrations is being reported; a further reason is that it was found to be associated with necrosis of the liver in the presence of ascaris infestation.

REPORT OF A CASE

A 2 year old Negro boy was admitted to the Children's Medical Ward of the University Hospital on Oct. 12, 1944, because of fever, loss of weight, cough, vomiting and diarrhea. He had been well until two weeks before admission, at which time he became feverish and listless and began to have five to six loose green stools per day. The diarrhea lasted for several days and was then followed by constipation and vomiting after meals. About five days before admission he began to have a productive cough, mostly nocturnal, and was given ammonium chloride, acetanalid and compound mixture of opium and glycyrrhiza.

The significant facts in his past medical history included eczema beginning at 2 weeks of age and lasting several months, "asthmatic bronchitis" and bronchopneumonia at 1 month and possible pertussis at 18 months. He lived in Florida from

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1. Loeffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk. **79**: 368, 1932.

2. Hodes, P. J., and Wood, F. C.: Eosinophilic Lung (Tropical Eosinophilia), Am. J. M. Sc. **210**:288 (Sept.) 1945. Apley, J., and Grant, G. H.: Tropical Eosinophilia as Seen in England, Lancet **1**:812 (June 30) 1945.

3. Soysa, E., and Jayawardena, M.: Pulmonary Ascariasis: A Possible Cause of Asthma, Brit. M. J. **1**:1 (Jan. 6) 1945.

his twelfth to his eighteenth month and is said to have ingested large quantities of "dirt" during that time. He was immunized against smallpox and diphtheria before he was 7 months of age.

The family history was noncontributory, although the father was alleged to have had a positive Wassermann reaction.

The physical examination on admission showed a pallid, sallow, irritable, light-haired colored boy, in acute distress, with a temperature of 104 F. a pulse rate of 132, a respiratory rate of 40, pale lips and conjunctivas, thin mucopurulent nasal discharge, injected pharynx, shotty inguinal and axillary lymph nodes, an enlarged liver which was palpable 4 cm. below the costal margin in the midclavicular line and transient rales in the area of the lower lobe of the right lung posteriorly. The spleen was not palpable and the heart was normal. An initial blood count showed a hemoglobin value of 35 per cent and white blood cell count of 40,000, with 37 per cent eosinophils.

TABLE 1.—*Hemolytic Observations*

Date	Transfusions	Hemoglobin, Percentage	White Blood Count	Eosinophils, Percentage	Total Eosinophils	Sedimentation Rate
9/12/44	.....	35	40,000	38	15,200	..
9/16/44	125 cc.					
9/29/44	125 cc.					
10/ 2/44	.....	52	16,500	31	5,115	..
10/ 3/44	130 cc.					
10/ 6/44	225 cc.					
10/12/44	.....	57	21,000	31	6,510	..
10/13/44	200 cc.					
10/15/44	225 cc.					
11/11/44	.....	65	40,000	62	21,200	..
11/14/44	75 cc.					
11/28/44	.....	64	92,000	76	70,000	85
12/ 7/44	130 cc.					
12/26/44	.....	62	50,200	79	40,000	..
12/30/44	300 cc.					
1/ 8/45	.....	71	58,000	79	46,000	..
1/24/45	.....	84	117,000	72	54,000	..
2/ 1/45	.....	77	35,000	..	.....	..
3/15/45	.....	65	35,000	79	27,700	..
3/28/45	.....	74	56,000	82	45,900	..
4/20/45	.....	65	36,000	84	30,200	90
4/28/45	.....	65	28,000	75	21,000	..
5/14/45	.....	77	12,500	70	8,750	75
6/11/45	.....	67	16,700	64	10,690	75
8/14/45	.....	69	12,700	26	3,300	65
10/ 1/45	.....	76	11,500	42	4,830	37
11/26/45	.....	78	8,800	16	1,410	30
1/11/46	.....	72	5,100	34	.....	36

The child's subsequent clinical course was characterized by septic fever for several weeks (his temperature rising to 103 to 104 F. each evening), by nocturnal cough, vomiting and distention, listlessness and anorexia. An early roentgenogram of the chest revealed "definite increase in the prominence of the pulmonary markings in both lung fields, which could be due in part to hypoventilation, but in addition to this showed some increased prominence of the pulmonary markings in the peritruncal region, particularly in the trunks in the lower lobe, roentgenologic observations which could support a diagnosis of Loeffler's syndrome in view of the high eosinophilia and the allergic history" (Dr. E. R. Pendergrass). The child was given a short course of penicillin but showed no demonstrable response. He was also given several small transfusions (table 1) in an effort to correct this anemia, which together with the eosinophilia remained unexplained in spite of the studies done.

The vomiting and distention did not seem to be relieved by conservative measures, and on October 21 an abdominal laporatomy was done to rule out an obstructive lesion in the right upper quadrant. At the operation the liver was found to be enlarged and to have small, gray-white lesions scattered over the smooth surface of all lobes. A biopsy was made (fig. 1 and fig. 2); there were focal necrotic lesions with numerous polymorphonuclear neutrophile and eosinophile leukocytes, and also numerous multinucleated giant cells. Shortly after the

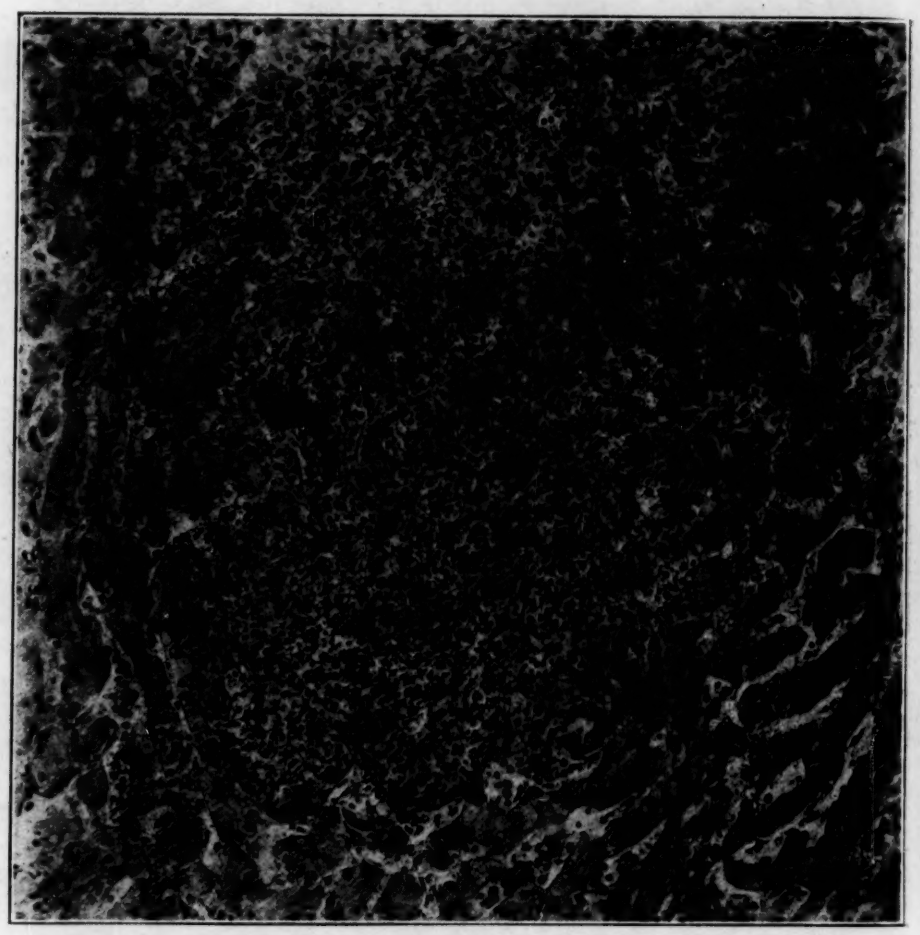

Fig. 1.—Photomicrograph of biopsy specimen of the liver made Oct. 21, 1944, before treatment with methionine, showing numerous neutrophile and eosinophile polymorphonuclear leukocytes. × 160.

operation, in an effort to protect the liver, administration of methionine [4] was started (3 Gm. three times a day). He was also given a high caloric, high protein diet, vitamin K, stable ferrous sulfate and the usual supplementary vitamins.

After the laparotomy the child began to improve. His cough subsided gradually, and the daily rise in temperature was somewhat lower than had been

4. The methionine was supplied by Wyeth Incorporated.

previously noted. On two occasions (October 22 and November 22) edema of the lips developed, each time lasting several days and not associated with edema elsewhere. By the end of November there was also a peculiar odor and hypertrichosis of the legs and arms. About this time his temperature became normal, and it remained entirely normal, except for an occasional infrequent rise to 101 F., until he was discharged in April 1945.

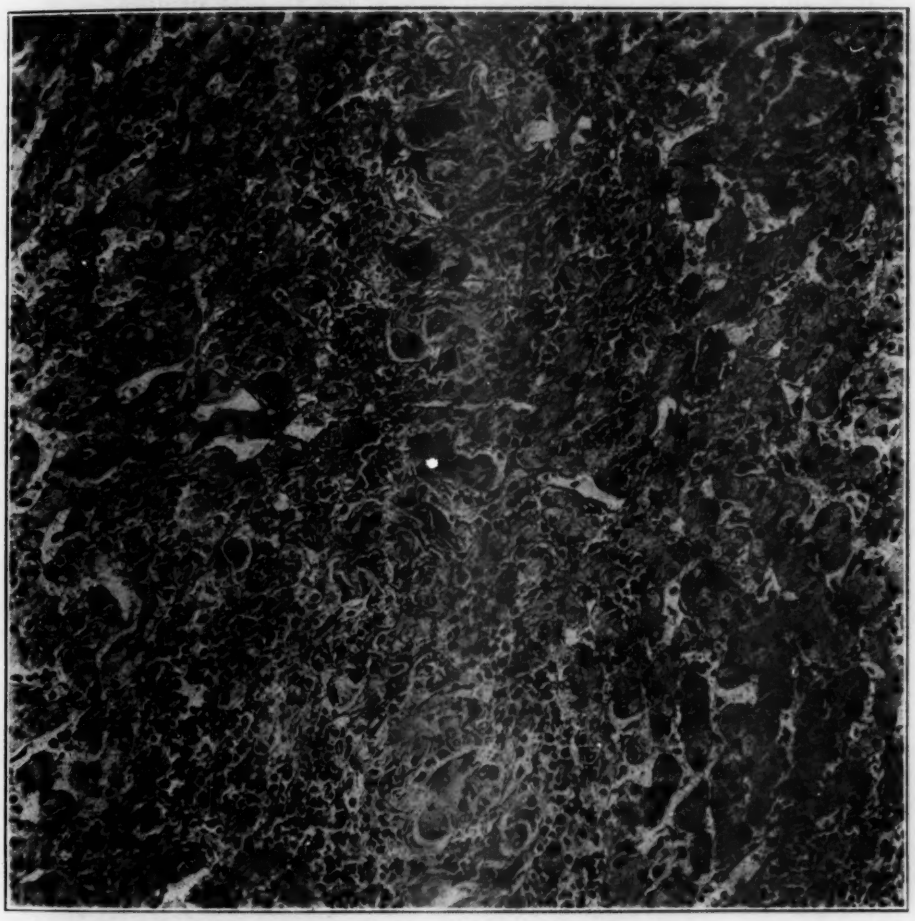

Fig. 2.—Photomicrograph of biopsy specimen of the liver made Oct. 21, 1944, before treatment with methionine, showing nodules containing numerous multinucleated giant cells. × 160.

On Dec. 23, 1944, the child vomited a single male adult ascaris, after which he improved remarkably, as evidenced by favorable changes in his behavior, activity and appetite. Administration of methionine was temporarily discontinued; it was started again on Jan. 23, 1945, and the drug was then given continuously throughout the rest of his hospital stay. Just prior to his discharge he was given the accepted treatment of hexylresorcinol for ascariasis.

On April 7 a second biopsy of the liver (table 2) was made; the hepatic tissue was found to be essentially normal, with few remaining necrotic lesions encapsulated by fibrous tissue. The roentgenogram of the chest at this time showed only a slight increase in the pulmonary markings. The child was discharged on April 28 in good condition, his hemoglobin having remained above 60 per cent since the time of his operation. His eosinophilia however, persisted, his total white cell count at discharge being 28,000, with 75 per cent eosinophils. His cough had not recurred. At the last visit, on Jan. 11, 1946, the child was in excellent condition, had been gaining weight steadily and was asymptomatic. His liver was barely palpable 1 cm. below the costal margin, the only abnormal finding being his moderate eosinophilia (table 1).

TABLE 2.—*Tests of Hepatic Function*

	Protein			Cephalin Flocculation		Cholesterol			Colloidal Gold	Bilirubin	
Date	Total	Albumin	Globulin	24 Hr.	48 Hr.	Total	Esters	Free			Comment
9/12/44	5.9	3.3	2.6	...	...	...	..	..	...	....	
10/21/44	...	...	...	...	...	...	..	..	...	....	Biopsy of liver
10/26/44	...	...	...	...	...	...	..	..	...	....	Methionine started, 1 Gm.
11/28/44	9.6	3.4	6.2	2+	3+	...	..	..	3+	0.17	
12/20/44	Hemolyzed			0.1+	1+	...	..	..	4+	....	Methionine discontinued
1/ 8/45	10.3	...	...	1.2+	2.3+	109	76	33	4+	....	
1/23/45	...	...	...	...	...	...	..	..	...	....	Methionine started again, 1 Gm.
2/14/45	9.6	3.0	6.6	3+	3.4+	130	74	56	3+	1.33	
3/ 8/45	8.8	3.8	5.0	0	2+	134	74	56	∓	....	
4/ 7/45	...	...	...	...	...	...	..	..	...	....	Biopsy of liver
4/26/45	...	...	...	...	...	...	..	..	...	....	Methionine discontinued
4/28/45	7.9	3.9	4.0	0	2+	143	..	..	1	0.26	
5/14/45	9.6	4.8	4.8	+	3+	...	..	..	0	0.16	
6/11/45	...	...	...	0	0	...	..	..	...	....	
8/14/45	8.4	4.9	3.5	0	∓	...	..	..	1+	0.49	
10/ 1/45	8.0	4.8	3.2	0	0	136	94	36	∓	0.16	
11/26/45	8.0	4.8	3.2	0	3+	...	..	..	0	0.18	
1/11/46	...	...	...	0	0	154	89	58	0	0.23	

All the observations with respect to the blood have been summarized in table 1, the studies on hepatic function in table 2 and the data from the electrophoretic analysis [5] in table 3.[6]

5. The electrophoretic analysis was done by Dr. Leslie A. Chambers, Johnson Foundation, School of Medicine, University of Pennsylvania.

6. Included in table 3 are average values for the various components of serum from a group of 30 normal men. Unfortunately, no such data are available for normal children in the age group of the patient. The runs for electrophoresis were conducted at 3.2 C. in borate-buffered sodium chloride solution of approximately 4.7 volts per centimeter. Measurements of the areas of separated components were made after one hundred and twenty minutes of electrophoresis, and the absolute areas were converted into concentrations expressed as grams per hundred cubic centimeters of undiluted serum, by utilization of conversion factors applicable to data from the particular instrument used. The concentrations indicated should be regarded as only approximate on an absolute basis, since numerous assumptions are involved in calibration of the instrument, but for comparative purposes the figures are informative.

The other studies done during hospitalization and after discharge did not reveal any essential abnormality, and included the following: biopsies of bone marrow, lymph node and muscle; repeated cultures of urine, feces, blood, duodenal drainage, pharyngeal and bronchial secretions, abdominal fluid and material aspirated from the liver; tuberculin tests in all dilutions; agglutination tests for typhoid, paratyphoid and Brucella abortus; intradermal tests for trichinosis, lymphogranuloma inguinale and echinococcosis; repeated examination of stool for ova and parasites; tests of swallowing function; roentgenograms of the long bones; repeated van den Bergh tests; fragility tests; platelet counts, and sickling tests.

TABLE 3.—*Composition of Serum Calculated from Electrophoretic Areas*

Date	Grams per Hundred Cubic Centimeters of Serum						Albumin-Globulin Ratio
	Albumin	α	β	γ	Total Globulin	Total Protein	
2/21/45	3.12	0.47	0.86	6.19	7.53	10.64	0.41
3/28/45	3.51	0.88	0.75	4.09	5.73	9.24	0.61
8/14/45	4.63	0.60	0.82	2.78	4.20	8.84	1.10
10/ 3/45	4.65	0.62	0.79	2.38	3.79	8.44	1.23
11/26/45	4.67	0.52	1.01	2.46	3.99	8.67	
1/11/46	4.59	0.68	0.74	2.42	3.84	8.33	1.20
Average normal (adult)	4.71	0.39	0.77	1.28	2.59	7.14	2.00

Blood counts and serologic tests for 1 sibling showed nothing abnormal. A bronchoscopic examination after the cough had subsided (on November 22) showed a hyperemic bronchial tree, and the secretions obtained at this time contained no ova or parasites, no eosinophils, lipoid material or tubercle bacilli. A cutaneous test with ascaris extract elicited a strongly positive reaction.

COMMENT

In reviewing this case in an attempt to arrive at a proper diagnosis, it becomes evident that the significant findings include a persistent, severe, but subsiding eosinophilia, minimal pulmonary changes, a septic fever of several months' duration, clearly demonstrable but reversible hepatic damage, an allergic background and infestation with Ascaris.

These findings and the clinical picture do not correspond exactly to any of the syndromes previously mentioned but when analyzed show easily discernible similarities; namely, eosinophilia, pulmonary changes, allergic phenomena and parasitic infestation.

In considering the etiologic factors in our case it is well to mention that parasitic infestation (with Ascaris,[7] liver fluke,[8] amebas,[9] Necator

7. Wild, O., and Loertscher, M.: Zur Aetiologie der flüchtigen Lungen-Infiltrierungen, Schweiz. med. Wchnschr. **64**:829 (Sept. 6) 1934. Zweitel, E.: Hautprüfungen mit Askaridenextrakt bei fluchtigen eosinophilen Lungen infiltraten, Helvet. med. acta **11**:117 (April) 1944.

8. Lavier, G.; Bariety, M., and Caroli, J.: Distomatose hépatique et syndrome de Loeffler, Paris méd. **1**:434 (May 20) 1939.

(Footnotes continued on next page)

Americanus [10]) and allergic reactions have been known to be of great importance in the syndromes which we have named. It is also interesting to note that the ascaris,[7] has been found to be the causative agent in many cases of Loeffler's syndrome and that Lavier [8] reported the presence of hepatitis in a case of Loeffler's syndrome due to infestation with liver flukes.

With these facts in mind it is not difficult to assume that the ascaris found in our case is of etiologic significance and that most of our findings, particularly the eosinophilia, pulmonary infiltrations, edema of the lips and necrosis of the liver, could well be explained on the basis of an allergic response to ascaris toxin. This thought becomes even more plausible when one recalls that the child showed definite allergic tendencies in his early months of life, that he had a strongly positive reaction to a cutaneous test with the ascaris toxin, and that he showed prolonged extensive elevations in gamma globulin well beyond the positive restoration of hepatic function. Other evidence in support of the allergic genesis, in contrast to mechanical and direct toxic factors, is the fact that no ova or parasites could be found in the fresh specimens or in microscopic sections of the liver, or in the sputum, bronchial secretions, duodenal drainage or feces. It is also interesting to point out here that Lavier [8] calls attention to the appearance of edema of the lips as an allergic response in his report of Loeffler's syndrome associated with hepatitis, that Meyer [11] also found edema of the face in a case of Loeffler's syndrome due to pollen, that Koino [12] himself contracted pneumonia after swallowing larval eggs of the ascaris and furthermore that Oldham and White [13] demonstrated a chronic interstitial hepatitis, "white spot liver" or "milk spot liver," in pigs who were fed ascaris eggs. True enough, Oldham and White found ascaris eggs in the liver and lungs and Koino had larvae in his sputum, but their experiments do not exactly simulate the natural course of the infestation of man by this parasite.

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9. Stefano, J.: Sindrome asmático per amebiasis pulmonar, Semana méd. **2**:749 (Sept. 28) 1939. Hoff, A., and Hicks, H. M.: Transient Pulmonary Infiltrations: A Case with Eosinophilia (Loeffler's Syndrome) Associated with Amoebiasis, Am. Rev. Tuberc. **45**:194 (Feb.) 1942.

10. Venzant Quintana, E.: Infiltrado de Loeffler, provocado por el Necator Americano, Rev. méd.-quir. de Oriente **3**:159 (Sept.) 1942.

11. Meyer, H. E.: Zur Kenntnis flüchtiger, mit Eosinophilie im Blut einhergehender Lungeninfiltrate, Med. Welt **11**:1808 (Dec. 25) 1937.

12. Koino, cited in Transitory Pulmonary Infiltrations Associated with Eosinophilia—Loeffler's Syndrome, editorial, J. A. M. A. **126**:837 (Nov. 25) 1944.

13. Oldham, J. N., and White, E. G.: Chronic Focal Interstitial Hepatitis in Pig: Its Experimental Production by Feeding Ascaris Eggs, J. Comp. Path. & Therap. **54**:1 (Jan.) 1944.

The other diagnoses considered were eosinophilic leukemia, familial eosinophilia, trichinosis, chronic brucellosis and tuberculosis, but these were excluded by the observations and studies made.

In further analyzing this case it was well to consider what possible role methionine played in protecting the liver, especially in view of the

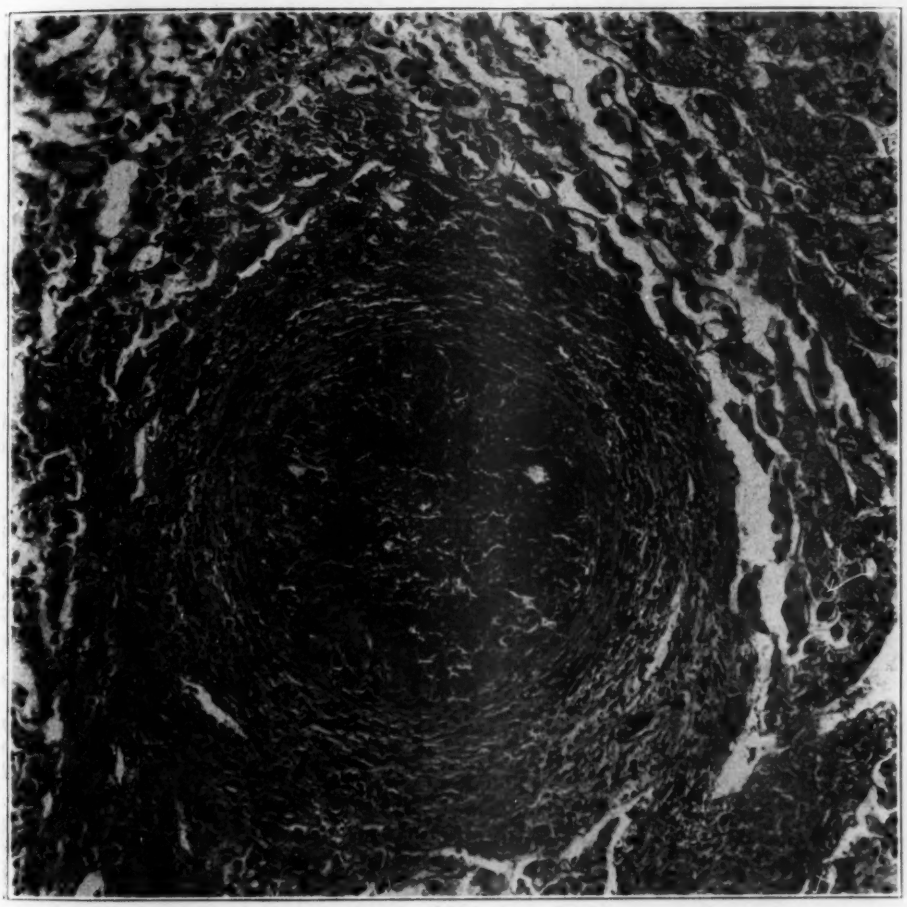

Fig. 3.—Photomicrograph of biopsy specimen of the liver made April 7, 1945, after treatment with methionine, showing focal necrotic lesion encapsulated by fibrous tissue. × 160.

fact that methionine has been reported to be efficacious in the treatment of dietary or toxic necrosis of the liver in animals [14] and in man.[15]

14. György, P.: Experimental Hepatic Injury, Am. J. Clin. Path. **14**:67 (Feb.) 1944.

15. Eddy, J. H., Jr.: Methionine in Treatment of Toxic Hepatitis, Am. J. M. Sc. **210**:374 (Sept.) 1945.

It was given by mouth, 1 Gm. daily for a period of two months, starting after the first biopsy. Treatment was temporarily discontinued because the reaction in the cephalin cholesterol flocculation test had returned almost to normal. When the flocculation test showed renewed deterioration in January, methionine medication was resumed in the same dosage and continued until the time of discharge. The improve-

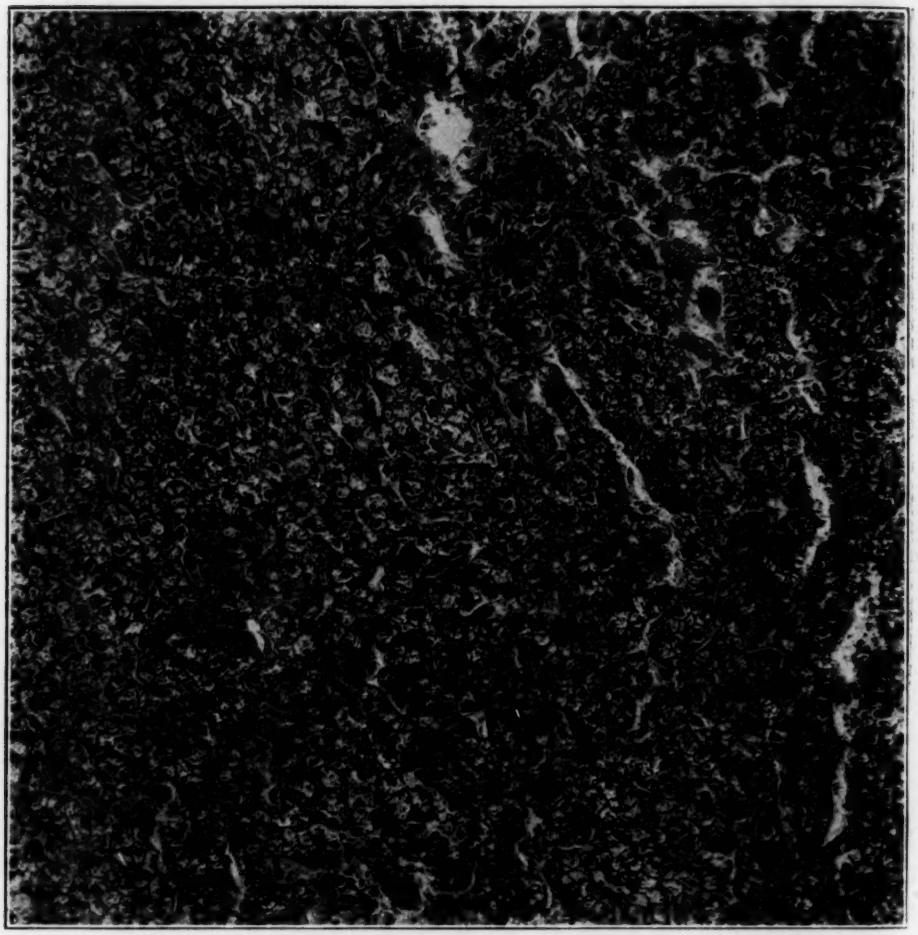

Fig. 4.—Photomicrograph of biopsy specimen of the liver made April 7, 1945, after treatment with methionine, showing essentially normal structure. × 160.

ment in the hepatic function became apparent from the colloidal gold test, even more distinctly than from the cephalin flocculation test. The slow decrease in the globulin values with corresponding rise in the albumin content was a further sign of convalescence. The second biopsy seemed to confirm all these observations in showing visible

improvement, both grossly and microscopically. Whether this improvement would have occurred without the administration of methionine cannot be definitely stated, but in view of the experimental work cited it seems that methionine could have been responsible for bringing about these changes. It might be stated here in regard to the effects of methionine that the hypertrichosis and distinctive odor previously mentioned have been known to occur in patients and animals receiving methionine and that both of these phenomena had completely disappeared by June 2, 1945, the odor having become less detectable even before that date.

Other observations worthy of note are the serologic reports, the sedimentation rate and the eosinophilia.

The serologic changes as listed in table 1 might well be considered to be a false positive reaction in view of the unusually high gamma globulin fraction noted in the electrophoretic pattern (table 1) and particularly since no stigmas of acquired or congenital syphilis could be found. The sedimentation rate was elevated initially and remained so for a long time but was approaching normal limits at the last examination.

A relatively moderate eosinophilia still persisted when the child was last seen, but this showed distinct improvement over the percentage and total number of eosinophils previously noted (fig. 3 and fig. 4). The eosinophilia noted in Loeffler's syndrome, tropical eosinophilia and pulmonary acariasis has been known to disappear while the patient was under treatment with arsenicals,[16] but in view of the child's apparent improvement and the hepatic damage found in the beginning of his illness it was considered inadvisable to give this type of therapy.

SUMMARY

The observations and clinical course of a case of chronic eosinophilia, anemia and transient pulmonary infiltrations with reversible focal necrosis of the liver in the presence of ascaris infestation are presented. Methionine was given in an effort to protect the liver, and improvement in hepatic function and in the findings at biopsy were noted.

16. Hodes and Wood.[2] Miller, H.: Transitory Lung Infiltration Accompanied by Eosinophilia, New England J. Med. **232**:7 (Jan. 4) 1945.

Case Reports

VARICELLA NEONATORUM

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PHILADELPHIA

INFECTIOUS diseases of the newborn have provoked much interest in the past. Our incomplete knowledge of neonatal immunity plus the added uncertainty of a variable incubation period and the role of the placenta make it difficult to comprehend some of the phenomena associated with such acute infectious diseases. Varicella is one of the diseases which infrequently affect the newborn. At least 10 such cases of varicella, are reported in the literature. The excellent report of Oppenheimer [1] is the only record we know of containing the report of a complete autopsy of this condition. Apert, as cited by Lereboullet,[2] is reported to have observed an epidemic of 12 cases of varicella in newborn infants 14, 16 and 17 days and older, with 2 deaths of premature infants, in whom autopsies showed the presence of tuberculous lesions. The youngest patient in whom varicella developed after birth is reported by Hubbard,[3] who described the appearance of typical varicella lesions in a 1 day old infant. Shuman [4] reported varicella in a baby two days after birth. Pridham [5] observed a newborn infant with an eruption (at birth) resembling what appeared to be the fourth day of varicella, a case in which the mother was only exposed to and did not have the disease. Others have described varicella in babies from 8 to 14 days of age, and in each case the disease was present in the mother from eight days before birth to one day after birth.

1. Oppenheimer, E. H.: Congenital Chickenpox with Disseminated Visceral Lesions, Bull. Johns Hopkins Hosp. **74**:240 (April) 1944.

2. Lereboullet: Varicelle du nouveau-né et du nourrisson, Rev. gén. de clin. et de thérap. **51**:97 (Feb. 13) 1937.

3. Hubbard, T. W.: Varicella Occurring in an Infant Twenty-Four Hours After Birth, Brit. M. J. **1**:822, 1878.

4. Shuman, H. H.: Varicella in the Newborn, Am. J. Dis. Child. **58**:564 (Sept.) 1939.

5. Pridham, F. C.: Chickenpox During Intrauterine Life, Brit. M. J. **1**:1054 (May 17) 1913.

Our interest in this subject was stimulated by 2 patients, 1 of whom was a premature infant. It is the purpose of this communication to present the cases of these patients, so that they may be added to the list of those already reported, and to discuss the clinical aspects, treatment and management of the premature infant and also the postmortem observations.

REPORT OF CASES

CASE 1.—G. M., a 26 year old Negro primigravida, was admitted to the Philadelphia Hospital for Contagious Diseases on May 17, 1942, with a history of having been pregnant for eight and one-half months. On May 14 she had noticed a crop of "pimples and blisters" on her face, which was followed by another crop of similar lesions on May 16. She had received antisyphilitic therapy given by a

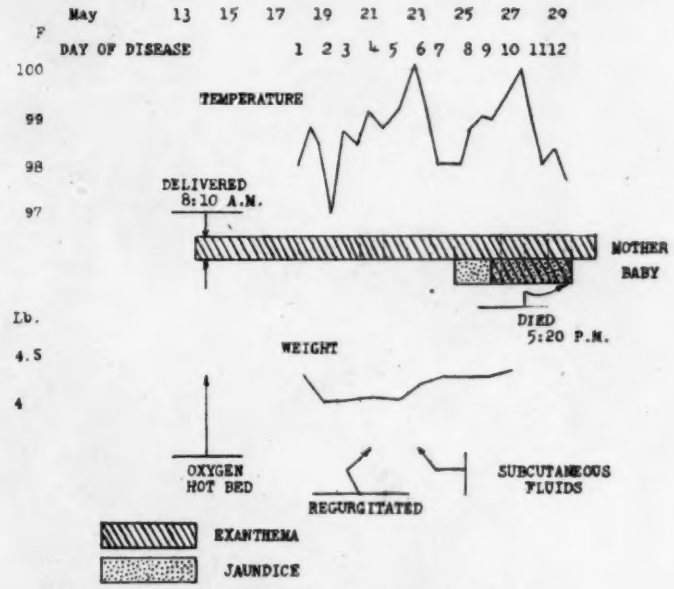

Fig. 1.—Clinical chart of Baby M. (case 1).

private physician several years before. On the day of admission she spontaneously delivered a 4 pound, 4¾ ounce (2,155 Gm.) girl. Except for signs of prematurity in the infant there were no other significant findings. The infant was first fed a formula of cow's milk, water and dextrimaltose, which was changed to feedings of mother's milk on the sixth day. She progressed satisfactorily and regained her birth weight by the eighth day. On May 24 she regurgitated a small amount of one of her feedings two times. On May 25, eight days after birth, generalized jaundice developed, and on May 26 at the age of 9 days she regurgitated for the third time; in a few hours there appeared a widespread eruption consisting of scattered macules and slightly elevated erythematous papules. Several vesicles containing a straw-colored fluid appeared on the face. The temperature was normal until one day after the appearance of the rash, when it rose to 100 F.; on the second day of the eruption it dropped to 95.6 F., the respirations becoming rapid and irregular, with intermittent periods of cyanosis. The vesicles on the forehead

coalesced, while the eruption on the torso became less intense, and the skin assumed a coppery hue. A yellow mucoid discharge appeared in the nose, mouth and vagina. The baby died on May 29, at the age of 12 days, on its third day of infection with varicella.

Laboratory Findings.—Results of a Wassermann (Kolmer-Kline) test of the blood on May 29 were negative. Results of a similar test given to the mother on January 16 and on May 18 were negative. On May 26 the hemoglobin content of the blood was 15 Gm. per hundred cubic centimeters, or 97 per cent. Red cells numbered 3,680,000 and white cells 6,720 per cubic millimeter, with 43 per cent

Fig. 2.—Section through the skin, showing typical vesicle formation and hyperplasia and hydropic degeneration of the contiguous cells. There is sparse mononuclear inflammatory response in the superficial corium.

polymorphonuclear leukocytes, 5 per cent monocytes, 50 per cent lymphocytes and 3 per cent eosinophils.

Dark field examination of fluid from a varicella vesicle and of secretions from the vagina, nose and throat (May 29) failed to reveal Treponema pallidum.

Postmortem Examination.—External examination of the body of Baby R. M. confirmed the presence of the maculopapular and vesicular eruption noted clinically.

The face was covered with pale, firm vesicles which exuded a clear watery fluid. Similar lesions were present over the remaining body surface, but they were much less numerous and intense. The umbilicus was clean and had healed completely. There were no gross congenital anomalies.

The abdominal cavity was healthy except for a slight enlargement of the liver.

The thymus was normal in size, position and consistency.

The heart showed nothing of gross pathologic significance other than patency of the foramen ovale. The ductus arteriosus was obliterated.

Fig. 3.—Oil immersion view of the skin, showing intranuclear inclusion bodies. These appear as a red-staining mass within the nucleus surrounded by a clear halo. The chromatin is condensed along the nuclear membrane. Roughly, at the bottom of the field there is a multinucleated giant cell containing the inclusion bodies.

The tracheobronchial tree contained a small amount of yellow-tinged frothy edema fluid in its lumen, but there was no gross evidence of atresia. Both lungs were poorly aerated and solid except for areas of crepitant tissue around the margins of all lobes. The solid areas were pinkish red and exuded a yellow frothy fluid on pressure.

The liver weighed 190 Gm. The organ was firm and on being sectioned revealed congestion and cloudy swelling.

The spleen showed moderate congestion.

The adrenal glands exhibited postmortem softening (the autopsy was performed sixty-nine hours after death).

The genitourinary tract presented nothing significant. Cortical surfaces of both kidneys were distinctly lobulated, a feature consistent with the subject's period of development.

Fig. 4.—A section of the lung, showing interstitial pneumonitis and an area of fibrinoid necrosis. Intranuclear inclusion bodies are present in some of the cells around the necrotic area but are not seen with this magnification.

The entire gastrointestinal tract was healthy. No vesicles were visualized on the mucosal surfaces, and no congenital anomalies were encountered.

The pancreas was normal to gross inspection and palpation.

Permission to open the head was refused.

The microscopic sections were interesting and enlightening.

The thymus, heart and kidneys presented evidence of prematurity compatible with the gestation period.

Slides containing sections of skin showed areas of hyperplasia and vesicle formation. The surface keratin was increased in amount and had a loose fibrillary appearance. In the regions of hyperplasia the component squamous cells were swollen, and their rete pegs were distorted. Their cytoplasmic outlines varied in appearance; in some areas the cytoplasm took the eosin stain faintly and in others it was completely vacuolated. In these vacuolated cells the nuclei were shrunken

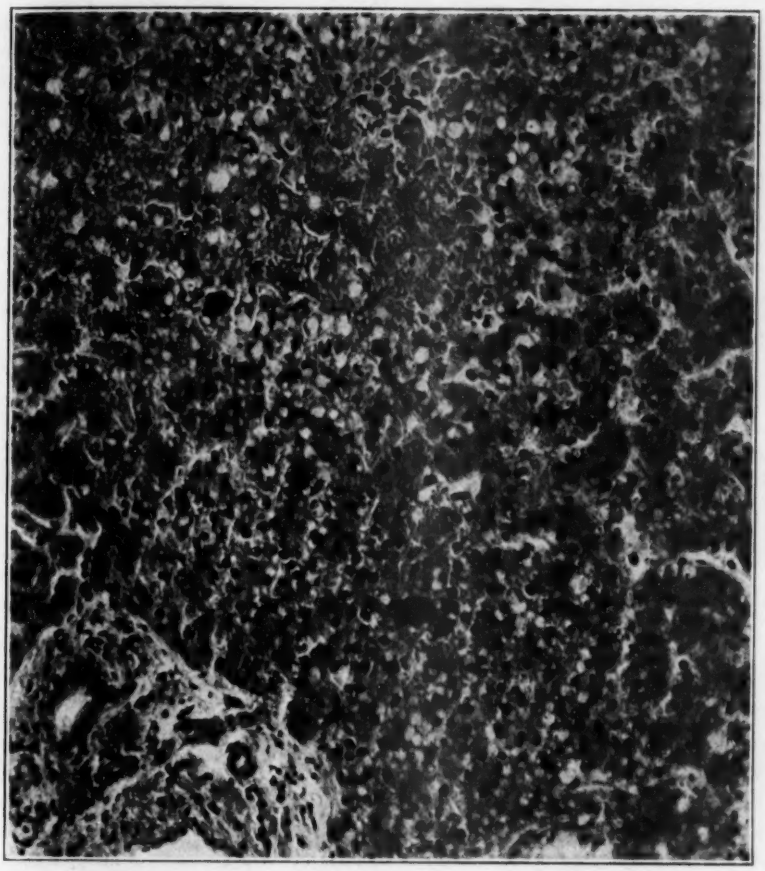

Fig. 5.—A section of the liver, showing granular degeneration and fatty metamorphosis. There is an area of fibrinoid necrosis in the upper portion of the field. These areas of necrosis were multiple and had a focal distribution.

and pyknotic, being pushed to the periphery and appearing as deep-staining spindled masses. In the faintly staining cells the nuclei were surrounded by a clear halo, although still occupying their normal central location. Within many of the nuclef there were fairly uniform, single, red-staining hyaline bodies surrounded by a clear space. These bodies appeared to push the chromatin nuclear material to the periphery so that it became aggregated as granular material on the nuclear mem-

brane. Here and there the nuclei merged together to form syncytial-like masses resembling giant cells. There were frequent areas of necrosis and of liquefaction of varying sizes which produced the gross vesiculation. These areas, however, tended to be superficial and in only a few places extended down to the basal layer. The dermis revealed mild edema and a sprinkling of mononuclear cells.

The lungs presented alveolar and interstitial edema. Most of the alveolar lumens contained pink-staining edema fluid and a few mononuclear cells which apparently represented sloughed-off lining cells. There was thickening of the alveolar walls by mononuclear inflammatory cells, the majority of which were lymphocytes. Scattered throughout the parenchymal tissue there were multiple foci of fibrinoid necrosis, none of which occupied more than one low power microscopic field. These foci were distributed chiefly around smaller bronchial branches and around blood vessels, occasionally extending into the walls of these structures.

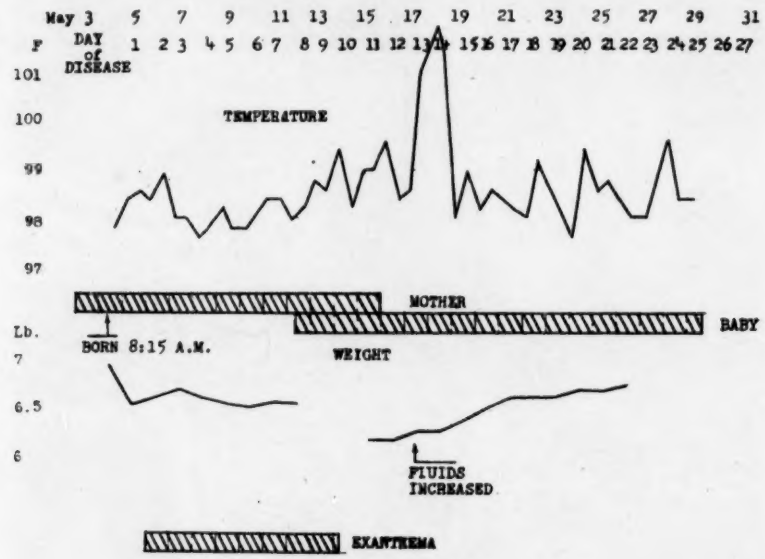

Fig. 6.—Clinical chart of Baby S. (case 2).

Within the necrotic areas there were numerous tiny pyknotic particles, and at the periphery, where the cells were still viable, intranuclear inclusions similar to those described for the skin were identified. The bronchi were filled with edema fluid. There was no evidence of congenital atelectasis or of the usual bronchopneumonic consolidation (fig. 4).

The liver showed fairly extensive damage. There was considerable congestion and fatty degeneration. A few aggregations of young red and white blood cells were encountered. There were numerous tiny areas of focal necrosis which bore no relationship to the normal lobular pattern occurring in the portal, midzonal and central areas. These areas were similar to those seen in the lungs except that few intranuclear inclusions were seen (fig. 5).

The spleen and adrenal glands were insignificant except for deep congestion and postmortem alteration.

No sections of the esophagus were taken at autopsy, but the stomach revealed hyperplasia and hypertrophy of its surface epithelium and a few tiny and superficial areas of necrosis associated with intranuclear inclusions.

The pancreas exhibited interstitial edema and a large area of hemopoiesis.

The cause of death after gross and microscopic examination was acute varicella with systemic involvement (fig. 6).

CASE 2.—On May 4, 1944, S. S., a 24 year old Negro septipara and her newborn infant were transferred to the Philadelphia Hospital for Contagious Diseases from a local general hospital because the mother had contracted varicella. There was a history of antisyphilitic therapy in 1943.

The baby weighed 6 pounds, 14½ ounces (3,245 Gm.) and was well developed and normal in appearance. She was fed an evaporated cow's milk formula. On May 12 at the age of 8 days characteristic varicella lesions developed over the abdomen and buttocks of the infant. Their appearance was preceded by a subnormal temperature for three days. At the time of the eruption she weighed 6 pounds 8½ ounces (2,950 Gm.), and she reached her ebb weight on May 15 three days later when she weighed 6 pounds, 5½ ounces (2,925 Gm.). She regained her birth weight at the age of 21 days. Results of a Wassermann test of the blood given to the baby on May 26 were negative.

COMMENT

The usual incubation period of varicella has been considered by most authorities to range between ten and twenty-one days [6]; however, Hubbard [3] has stated it to be from three to four days and Gregory, cited by Cecil,[6a] held that it is from four to seven days. Steiner cited by Abt,[6b] by inoculation of human subjects, has demonstrated it to be eight days. In the newborn infant there are several factors which may affect the length of the incubation period. Exposure of the fetus may occur at one of three times: (1) at the time of the original exposure of the mother; (2) at the time of the onset of varicella in the mother, or (3) by contact with the mother at the time of delivery.

The rash appeared nine days after birth in case 1. However, jaundice preceded the rash by twenty-four hours in this patient. Exposure occurred at one of the following times: (*a*) at the time of the original exposure of mother, which would necessarily be more

6. (*a*) Cecil, R. L.: A Text-Book of Medicine, ed 2, Philadelphia, W. B. Saunders Company, 1930, p. 317. (*b*) Abt, I. A.: Pediatrics, ibid., 1926, vol. 6, p. 200. (*c*) Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood, revised by L. E. Holt Jr. and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1936, p. 931. (*d*) Griffith, J. P. C.: Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1919, vol. 1, p. 383. (*e*) Jeans, P. C.: The Communicable Diseases, Iowa City, Iowa, University Multigraph Department, 1931, p. 17. (*f*) Grulee, C. G., and Bonar, B. E.: The Newborn: Diseases and Abnormalities, New York, D. Appleton and Company, 1926, vol. 3, p. 23. (*g*) Osler, W.: The Principles and Practice of Medicine, ibid., 1930. (*h*) Stimson, P. M.: A Manual of the Common Contagious Diseases, ed. 3. Philadelphia, Lea & Febiger, 1940.

than twelve days; (*b*) at the onset of varicella in the mother, which would make the incubation period twelve days; (*c*) during delivery, making the incubation period nine days.

In case 2 (*a*) the interval between the original exposure of mother and the onset of varicella in the newborn infant would necessarily be more than nine days; (*b*) the interval from the time of onset of the disease in the mother to the onset in the infant nine days, and (*c*) the interval from the time of birth to the onset eight days.

The intervals between the onset of disease in the mothers and the appearance of the disease in the newborn infants in our cases were twelve days and nine days respectively. The onset of varicella at nine days after birth in case 1 and at eight days in case 2 indicates that the fetuses could have been exposed during delivery. This incubation period compares with Steiner's case of varicella, in which the onset occurred eight days after the intentional inoculation of the patient. It is therefore

Cases of Manifest Varicella in Mother and Newborn Reported by Various Authors

Author	Onset in Mother	Onset in Baby, Days After Birth	Comment
Hubbard,[3] 1878.....	None, exposed only	2	
Pridham,[5] 1913.....	None, exposed only	4 days before birth	
Moricand, 1913, cited by Lereboullet [2]	1 day before delivery	14	
Henderson, W. B.: J. Pediat. 4 : 668, 1934	Day of delivery	8	
Baron, F.: Nourrisson 23 : 157, 1935	Day of delivery	8	Died on twelfth day
Shuman,[4] 1939.....	8 days before delivery	8	
Campbell, E. P.: Am. J. Dis. Child. 57 : 1408 (June) 1939	1 day after delivery	12	
Oppenheimer,[1] 1944.....	5 days before delivery	7	Died on eleventh day

suggested that the exposure of the fetuses probably occurred either (1) when the disease became manifest in the mother or (2) during delivery.

Although the presence of endometrial varicella lesions has never been reported, it may be assumed that since varicella lesions are disseminated throughout the body these lesions may also involve the endometrium with inoculation of the fetal membranes and the fetus. If this assumption is correct, "then in utero" infection does not necessarily imply that fetal infection follows transplacental transmission of the virus. The fact that variola may be congenital[7] indicates that transplacental transfer of the virus may occur. By a similar mechanism the fetus may be infected with the varicella virus, as may have occurred in Pridham's and Hubbard's patients.

The order of appearance and distribution of the eruption is similar to that seen in children and in adults, namely, appearing first on the

7. Schamberg, J. F., and Kolmer, J. A.: Acute Infectious Diseases, Philadelphia, Lea & Febiger, 1928, p. 159.

torso and then spreading centrifugally. The vesicles are less tense and less resistant to rupturing than they are in older patients. Pustulation, which sometimes occurs in older patients, did not occur in our babies.

The presence of jaundice noted in case 1 twenty-four hours prior to the visible cutaneous eruption suggests that hepatic involvement, as well as widespread visceral involvement, which was confirmed at necropsy, may be one of the earlier manifestations of the disease. It is possible that the skin may be simultaneously affected but that it requires a longer time for the lesions to become visible.

The observations at autopsy in case 1 are of particular interest from the pathologic standpoint, not because they add anything to the literature, which has been covered adequately by Oppenheimer [1] recently and by Johnson [8] and Schleussing,[9] but because of the striking difference between the gross and the microscopic appearances. At autopsy the skin and lungs showed significant pathologic changes, but on microscopic study lesions were also found in the liver and the stomach. However, this is readily understandable, because both the hepatic and the gastric lesions, while diffuse, were of microscopic size. Unfortunately, we were unable to examine the brain of this patient because of restricted permission for autopsy. Our case (case 1) differs from those reported by Oppenheimer [1] and Johnson [8] in that the systemic involvement in our patient was limited to the lungs, liver and gastrointestinal tract, whereas in their patient the systemic manifestations were more generalized. Schleussing's patient apparently lacked the intranuclear inclusions which were readily discernible in our patient. The epidermal inclusions were similar to those described by Tyzzer [10] and later labeled type A inclusions by Cowdry.[11]

As Smith and Gault [12] have pointed out, the basic lesions appear to be located intracutaneously or in the mucous membrane, with systemic involvement in the severe forms of the disease, such as varicella gangrenosa.

Our patient (case 1) exhibited histologic evidence of prematurity, a manifestation which was compatible with the stage of gestation. The focal areas of necrosis were multiple in the skin, lungs, liver and stomach and were associated with intranuclear inclusions. No bacterial colonies

8. Johnson, H. N.: Visceral Lesions Associated with Varicella, Arch. Path. **30**:292 (July) 1940.

9. Schleussing, H.: Nekrosen in Leber, Milz und Nebennieren bei nicht vereiterten Varizellen, Verhandl. d. deutsch. path. Gesellsch. **22**:288, 1927.

10. Tyzzer, E. E.: The Histology of the Skin in Varicella, Philippine J. Sc. **1**:349, 1906.

11. Cowdry, E. V.: Problem of Intranuclear Inclusions in Virus Diseases, Arch. Path. **18**:527 (Oct.) 1934.

12. Smith, L. W., and Gault, E. S.: Essentials of Pathology, ed. 2, New York, D. Appleton-Century Company, Inc., 1942, p. 185.

were visualized, and there was little inflammatory cellular infiltration except as noted in the skin and lungs. Oppenheimer [1] described neutrophilic invasion of the dermis in her report. The dermis of our patient showed a sprinkling of mononuclear cells. The interstitial pneumonitis is compatible with virus disease of the lungs. The jaundice noted clinically can be explained by the extensive hepatic damage. There was no histologic evidence of tuberculosis such as was seen in Apert's series of cases mentioned by Lereboullet,[2] although the areas of necrosis in the liver did have a caseous appearance.

The histologic picture confirms the already known fact that chickenpox is a virus disease affecting chiefly epithelial structures.

TREATMENT AND MANAGEMENT

It is doubtful whether immediate removal and isolation of the newborn infant would have prevented the disease, since delivery occurred after the onset of the disease in the mother. It is advisable to administer convalescent serum prophylactically to the baby when it is known or suspected that the mother has recently been exposed or when she comes down with the disease after parturition. There is no specific therapy for varicella, and the use of various serums is of questionable value once the disease manifests itself. Treatment is directed toward the prevention of secondary dermal and pulmonary infections, maintenance of fluid balance and adequate caloric intake. Premature infants require the usual meticulous nursing and feeding care. Breast feedings should be withheld in order to minimize exposure which would otherwise be continued by contact with the breast and breast milk.

SUMMARY

In 2 cases of congenital varicella the exanthema developed in 1 patient on the ninth day and in the other on the eighth day after birth.

The disease clinically is not unlike that which appears in older patients.

The appearance of jaundice twenty-four hours before the exanthema in 1 patient may indicate the presence of visceral involvement before the appearance of cutaneous lesions.

Treatment is symptomatic.

Observations at autopsy on the premature infant indicated widely disseminated visceral lesions in the lungs, liver and gastrointestinal tract, associated with the usual cutaneous changes. These lesions were characterized by multiple areas of focal necrosis and by intranuclear inclusions.

Dr. E. S. Gault, Associate Professor of Pathology and Parasitology, Temple University Medical School, permitted us to use the photomicrographs.

Progress in Pediatrics

TERTIAN, QUARTAN AND MIXED MALARIAL INFECTIONS

A Survey of Three Hundred and Thirty-Four Cases of Infection with Plasmodium Vivax, Ten Cases of Infection with Plasmodium Malariae and Eight Cases of Mixed Malarial Infections in Children

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ALTHOUGH the disease entities which one meets on the Isthmus of Panama are similar to those encountered in temperate zones, their incidence is altered by climate, mode of living and sanitary conditions. This difference is particularly emphasized in the practice of pediatrics in Panama, where a pediatrician cannot help being impressed with the frequency of the malarial fevers and intestinal helminthiasis in children. Instead of being of minor medical importance, as they are in most parts of the United States, these infections are so prevalent as to be matters of prime clinical significance. Studies of helminthiasis and malaria on the Isthmus of Panama were undertaken. Reports dealing with the common intestinal parasites observed here have been published elsewhere.[1]

Relatively little of the extensive literature on malaria deals with the effects of the disease on children. In some reports, it is suggested that malaria in children is similar to malaria in adults. This has not been borne out by clinical observation. Misconceptions concerning the incidence, clinical manifestations and treatment of malaria in children prompted this survey.

From the Pediatric Services, Gorgas and Colon Hospitals, Ancon and Cristobal, Canal Zone.

1. Miller, J. F., and Einhorn, N. H.: Oxyuriasis: A Clinical Survey of Two Hundred Consecutive Cases of Infection with Enterobius Vermicularis in Children, Am. J. Dis. Child. **68**:376-381 (Dec.) 1944. Einhorn, N. H.; Miller, J. F., and Whittier, L.: Ascariasis: Clinical Survey of One Hundred and Twenty-Five Cases of Infection with Ascaris Lumbricoides in Children, ibid. **69**:237-246 (April) 1945. Miller, J. F.; Einhorn, N. H., and Whittier, L.: Ancylostomiasis and Strongyloidiasis: A Clinical Survey of Seventy-One Cases of Ancylostomiasis and Eleven Cases of Strongyloidiasis in Children, ibid. **69**:359-365 (June) 1945. Einhorn, N. H.; Miller, J. F., and Whittier, L.: Intestinal Polyparasitism: Clinical Survey of One Hundred and Sixty-One Cases of Infection with Multiple Intestinal Parasites in Children, ibid. **69**:350-358 (June) 1945. Whittier, L.; Einhorn, N. H., and Miller, J. F.: Trichuriasis in Children: A Clinical Survey of Fifty Cases and Reports of Three Cases with Heavy Infection and Striking Clinical Symptoms, ibid. **70**:289 (Nov.-Dec.) 1945.

SOURCE OF MATERIAL

This study is one of three surveys based on investigations of patients with malaria admitted to the pediatric wards of Gorgas Hospital, Ancon, and Colon Hospital, Cristobal, Canal Zone, between July 1, 1939, and July 1, 1945. During this period 845 children were treated for malaria in these hospitals. Five hundred and eighty-four were treated at Gorgas Hospital, and 261 were treated at Colon Hospital.

The patients were divided into four groups as follows: group 1, 493 children infected with Plasmodium falciparum; group 2, 334 children infected with Plasmodium vivax; group 3, 10 children infected with Plasmodium malariae and group 4, 8 children with mixed infections. Group 1 has been reported in a separate communication.[2] The present study is based on observations on the second, third and fourth groups.

In the Canal Zone there exists a system of state medicine among government employees and their families; therefore, no socioeconomic selection of patients was made in this series, and all groups were represented. Racially, the patients were classified as white, Negro and mestizo. The term race as used in this paper connotes a collection of persons with similar antecedents, customs, language and appearance.

P. VIVAX MALARIA

EPIDEMIOLOGIC CONSIDERATIONS

Season.—The Canal Zone is located between latitude 8° 50′ and 9° 25′ north, and between longitude 79° 30′ and 80° 5′ west. The climate is tropical, with an average relative humidity of 83 per cent,[3] heavy rainfall, a short dry season extending from January through April and a long wet season extending from May through December. The yearly rainfall is not equal in all parts of the Canal Zone. On the Atlantic side, where Colon Hospital is located, precipitation is about twice as much as on the Pacific side, where Gorgas Hospital is located. The terrain is hilly and mountainous in some parts, numerous streams are present, and vegetation is dense and luxuriant. During the height of the rainy season, the streams are full, rapid and prone to floods, thus offering little opportunity for propagation of the mosquito. When the change of season occurs and during the dry season, many streams become pools or collections of stagnant water which provide ideal breeding places for mosquitoes. Breeding continues throughout the entire year, although

2. Einhorn, N. H., and Tomlinson, W. J.: Estivoautumnal (Plasmodium Falciparum) Malaria: A Survey of Four Hundred and Ninety-Three Cases of Infection with Plasmodium Falciparum in Children, Am. J. Dis. Child. **72**:137 (Aug.) 1946.

3. Annual Meteorological Reports, Panama Canal, Department of Operation and Maintenance, Section of Surveys, Mount Hope, Canal Zone, Panama Canal Press, 1939-1945.

in most localities it is reduced during the height of the dry season, when the number of breeding places is greatly reduced.

The number of cases of malaria varied from year to year and from month to month. The largest numbers were seen in 1940, 1942 and

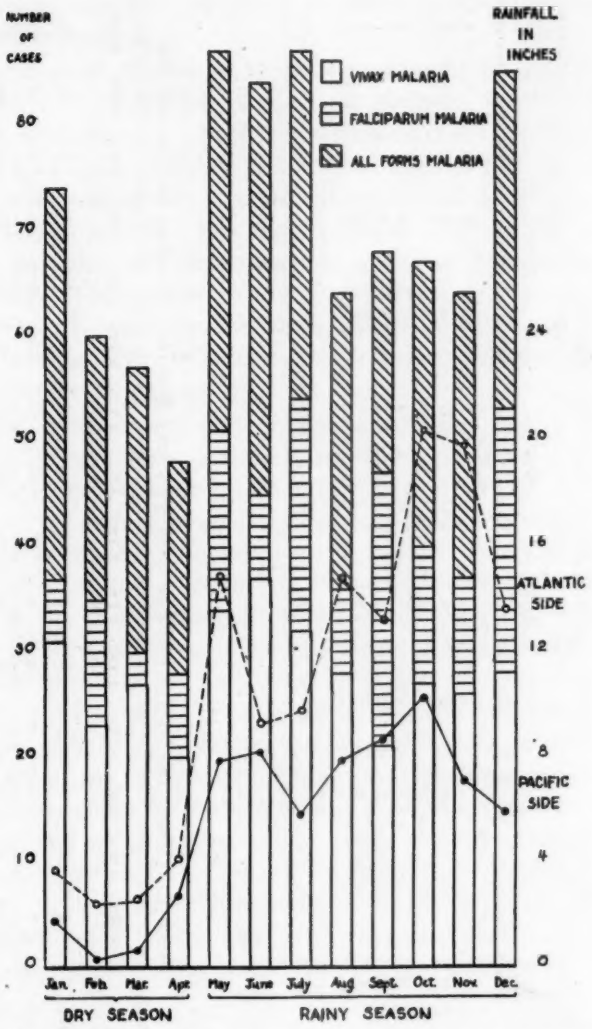


Fig. 1.—Seasonal frequency of P. vivax malaria, P. falciparum malaria and all forms of malaria combined.

1944; the smallest number was seen in 1943 (table 1). Cases were observed in every month of the six years covered by this survey. The smallest number of cases was seen during the height of the dry season extending through the months of February, March and April, while

TABLE 1.—*Incidence of P. Vivax Malaria*

Year	Month												Total
	January	February	March	April	May	June	July	August	September	October	November	December	
1939	..	..	..	..	..	..	2	2	3	3	4	5	19
1940	6	3	6	5	4	12	12	5	5	7	5	3	73
1941	2	4	5	4	6	4	6	2	1	5	5	7	51
1942	2	4	2	3	9	10	2	3	4	4	4	5	52
1943	2	1	7	2	4	1	7	6	1	4	7	2	44
1944	8	4	2	3	2	4	3	10	7	4	1	6	54
1945	11	7	5	3	9	6	..	..	..	..	..	..	41
Total	31	23	27	20	34	37	32	28	21	27	26	28	334

TABLE 2.—*Distribution of 334 Children with P. Vivax Malaria, According to Age and Sex*

Age	3 Mo.	6 Mo.	9 Mo.	1 Yr.	1 Yr. 3 Mo.	1 Yr. 6 Mo.	2 Yr.	3 Yr.	4 Yr.	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	Total
Boys	1	2	1	6	2	6	15	16	15	18	26	15	9	14	11	12	17	186
Girls	1	2	2	5	4	8	17	10	13	13	21	8	9	8	10	10	7	148
Total	2	4	3	11	6	14	32	26	28	31	47	23	18	22	21	22	24	334

the largest number was seen at the beginning and end of the rainy season during the months of May, June, July and December (fig. 1). The months of May and December marked the beginning and the end of the rainy season, when the small amount of precipitation was sufficient to create puddles of stagnant water but insufficient to flush out larvae. These collections of water provided excellent breeding places for anopheline mosquitoes.

From the point of view of sanitation, communities on the Isthmus of Panama are (1) sanitated, (2) partially sanitated or (3) unsanitated. Essentially, sanitation consists of the destruction of the anopheline vectors of malaria and their breeding places; the protection of man from the bites of these vectors and the destruction of Plasmodia in infected persons. It was observed that the number of children who contracted malaria in partially sanitated areas was almost as large as the number who contracted it in completely unsanitated areas. For purposes of this report, therefore, partially sanitated districts were not considered separately and patients who came from either unsanitated or partially sanitated areas were grouped together.

Location and Character of Dwellings.—Living conditions on the Isthmus of Panama were separated into three types as follows: (1) United States government communities located in the Canal Zone, characterized by minimal crowding, excellent toilet and sewage disposal facilities, paved streets, landscaped yards and complete sanitation; (2) principal cities of the Republic of Panama (Colon and the City of Panama), in the center of which overcrowding among the poor is commonplace, facilities for sewage disposal are adequate, although not used to the fullest extent by an uninformed populace, and streets and alleys are paved; in the outskirts of these cities, however, facilities for sewage disposal are minimal, the streets are unpaved, and landscaping and sanitation are absent; (3) rural or semirural communities in the Canal Zone or the Republic of Panama (interior), where population is sparse, living conditions are primitive, homes are of the open thatched variety and little or no attempt at screening or sanitation is made.

In order to determine the relation of location and type of dwelling to the incidence of P. vivax malaria, the available data from this series of 334 children were analyzed, with the following results:

	Number of Patients	Per Cent
United States government communities.....	55	16.5
Principal cities of the Republic of Panama	40	11.9
Rural or semirural communities.....	239	71.6
Total.....	334	100.0

It was surprising to observe that 95, or 28.4 per cent of the patients, came from sanitated communities in the Canal Zone and Republic of Panama. Although trained workers investigated all cases reported

from sanitated areas, it was not possible to trace the origin of infections in this group of 95 children to unsanitated areas. Furthermore, there was no way of determining how many of these patients were bitten by stray mosquitoes blown over into sanitated areas, or how many were bitten during their wanderings in unsanitated areas. The 334 patients with P. vivax malaria named ninety communities as their homes. One hundred and thirty-six, or 40.7 per cent, of these children came from nine, or 10 per cent, of the communities named. Thirty-three, or 9.9 per cent, came from the native village of Chilibre and 26, or 7.8 per cent, came from the village of Chiva Chiva, indicating that some areas are more definitely reservoirs of infection than others.

Age.—The age distribution is shown in table 2. The youngest patient was a 6 week old infant in whom P. vivax malaria developed twelve days after a transfusion of blood. Her mother served as the donor. There were 2 infants under the age of 2 months. Twenty, or 6 per cent, had had their first attack by the end of their first year of life, and an additional 52, or 15.6 per cent, had had their first attack by the end of the second year. Thus, by the end of the second year of life 21.6 per cent, or more than one fifth of the children, had had at least one attack of P. vivax malaria. With the exception of the age of 6 years, when a large number of cases occurred, the incidence per year of life from the age of 2 to 12 years was uniformly high.

Sex.—One hundred and eighty-six, or 55.7 per cent, were boys and 148, or 44.3 per cent, girls (table 2).

Race.—Two hundred and forty-two of the patients, or 72.5 per cent, were mestizo; 65, or 19.5 per cent, were Negro, and 27, or 8 per cent, were white. These striking differences were closely related to the habitations of the patients. All of the white and a few of the mestizo patients lived where sanitation was entirely satisfactory. Many of the Negroes lived where sanitation and environmental factors were only fairly satisfactory. A few of the Negro as well as most of the mestizo children actually lived on the soil, in thatched and unscreened huts located in completely unsanitated areas. Fifteen, or 55.6 per cent, of the 27 white children acquired P. vivax malaria after a single trip into the interior of the Republic of Panama.

SYMPTOMATOLOGY OF P. VIVAX MALARIA

The following questions were answered carefully before the symptoms and physical signs presented by each child were analyzed: Was the present attack the first attack of malaria; if not, when and of what type was the last attack and were any of the symptoms observed due to the presence of associated unrelated diseases? In order to answer the questions relating to the number of attacks experienced by each child, the 334

cases of P. vivax malaria were classified into four groups as follows: (1) primary malaria, (2) questionable primary malaria, (3) recurrent malaria and (4) questionable recurrent malaria.

One hundred and twenty-four patients with primary malaria satisfied three or more of the following criteria: (1) no history of a previous attack of malaria, (2) residence either in a sanitated area or for less than six weeks in an unsanitated area, (3) no history of a recent trip into an unsanitated area and (4) absence of physical signs attributable to a previous attack of malaria.

Thirty-eight patients with questionable primary malaria satisfied two or more of the following criteria: (1) no history of a previous attack of malaria; (2) prolonged residence in an unsanitated area, indicating the possibility of previous or constant exposure to malarial infection, and (3) absence of physical signs attributable to a previous attack of malaria.

TABLE 3.—*Associated Unrelated Diseases in 334 Children with P. Vivax Malaria*

Disease		Number of Patients
Intestinal helminthiasis		117
Diseases of the respiratory tract		4
Asthma	2	
Childhood tuberculosis	1	
Pneumonia	1	
Acute communicable disease		2
Paradysentery Shigella		1
Paratyphoid		1
Acute glomerulonephritis		1
Miscellaneous		1
Total		127
P. vivax malaria, unassociated		207

Sixty-seven patients with recurrent malaria satisfied one of the following criteria: (1) presence of a definite history of a previous attack of malaria within a period of less than one year without new exposure or (2) a history of either a previous attack of malaria or of bouts of fever of undetermined origin within a period of over one year with physical signs attributable to a previous attack of malaria.

One hundred and five patients with questionable recurrent malaria satisfied one or more of the following criteria: (1) history of a previous attack of malaria or of bouts of fever of undetermined origin with or without a history of response to antimalarial therapy, (2) no definite history of a previous attack of malaria in a patient whose prolonged residence in an unsanitated area indicated the probability of previous or constant exposure to malarial infection and (3) presence of physical signs attributable to a previous attack of malaria.

One hundred and twenty-seven children, or 38 per cent, had conditions in addition to malaria, and 207, or 62 per cent, had symptoms accounted for by malaria alone (table 3). Of the unrelated associated

diseases encountered, helminthiasis and miscellaneous conditions of the respiratory tract were most frequent, with a total of 117 patients (35 per cent) and 4 patients (1.2 per cent), respectively. The helminths commonly observed were Ascaris lumbricoides, Trichuris trichiura, Strongyloides stercoralis and the hookworms.

Symptoms were divided into three classes as follows: (1) those presumably due to P. vivax malaria, (2) those due to either malaria or associated unrelated disease and (3) those due to associated unrelated disease. The third group included such complaints as otorrhea, rash, rhinorrhea and sore throat. This large aggregate seemed to bear no obvious relation to P. vivax malaria; hence it was eliminated from consideration. The second group—those attributable either to malaria or to

TABLE 4.—*Symptomatology of P. Vivax Malaria*

Symptoms	Type of Malaria									
	Primary		Questionable Primary		Recurrent		Questionable Recurrent		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Fever	47	37.9	26	68.4	47	70.1	56	53.3	176	52.7
Chills and fever	75	60.5	12	31.6	18	26.9	48	45.7	153	45.8
Vomiting	60	48.4	17	44.7	29	43.3	40	38.1	146	43.7
Headache	36	29.0	17	44.7	27	40.3	29	27.6	109	32.6
Anorexia	28	22.6	9	23.7	13	19.4	30	28.6	80	24.0
Cough	24	19.4	6	15.8	13	19.4	31	29.5	74	22.2
Abdominal pain	11	8.9	7	18.4	11	16.4	8	7.6	37	11.1
Somatic pain	7	5.6	6	15.8	7	10.4	12	11.4	32	9.6
Diarrhea	9	7.3	1	2.6	3	4.5	5	4.8	18	5.4
Convulsions	6	4.8	1	2.6	4	6.0	6	5.7	17	5.1
Malaise	7	5.6	0	0.0	7	10.4	1	1.0	15	4.5
Fretfulness, irritability, restlessness	2	1.6	2	5.3	2	3.0	3	2.9	9	2.7
Delirium, stupor	4	3.2	0	0.0	2	3.0	3	2.9	9	2.7
Constipation	3	2.4	0	0.0	0	0.0	1	1.0	4	1.2
Drowsiness, listlessness	2	1.6	0	0.0	0	0.0	0	0.0	2	0.6
Loss of weight	0	0.0	0	0.0	0	0.0	1	1.0	1	0.3
Pain in chest	0	0.0	1	2.6	0	0.0	0	0.0	1	0.3
Vertigo	0	0.0	0	0.0	0	0.0	1	1.0	1	0.3
Weakness	0	0.0	0	0.0	0	0.0	1	1.0	1	0.3

associated unrelated disease—could not be eliminated without introducing the possibility of discarding important and relevant findings. In order to avoid missing significant clinical findings, the first and second groups were combined (table 4).

The typical paroxysm, consisting of chill, fever and sweat or the "cold," "hot" and "sweating stages," was observed no more frequently in tertian than it was in P. falciparum malaria.[2] Prodromal symptoms such as anorexia, headache, irritability and malaise existed frequently and from one to four days before the onset of acute symptoms. The sudden onset with chill, fever and prostration without prodromes occurred in 91, or 27.2 per cent, of the patients. In children under the age of 3 years, typical paroxysms with distinct cold, hot and sweating stages were uncommon. These stages when present in older children with P. vivax malaria seemed to be more characteristic than those

observed in P. falciparum malaria. However, symptoms usually associated with one stage of the paroxysm were often observed in other stages.

Cold Stage.—All the temperatures recorded in this study were taken rectally. Fever, chills and fever, and vomiting were the most frequent symptoms, occurring in 52.7, 45.8 and 43.7 per cent of the patients, respectively. Thus fever with or without chill was the commonest finding, having been observed in 98.5 per cent of the patients. The chill, which was absent in slightly more than one half of the patients, seemed to be replaced frequently by vomiting or convulsions followed by fever. Older patients often complained of chilliness and of cold extremities. The chill was usually ushered in by a feeling of chilliness, which was followed quickly by an actual chill with chattering teeth and a generalized shaking of the body. Although the temperature rose steadily, the older children complained of being cold throughout the cold stage. The facial features were pinched; varying degrees of cyanosis of the lobes of the ears, lips, face, hands and feet were present, and the surface of the body seemed dry and cold. The pulse was rapid, weak and often irregular. The cold stage lasted from twenty to sixty minutes and was followed by the hot stage.

Hot Stage.—The temperature, which rose gradually during the cold stage, reached a peak during the hot stage. Although maximum temperatures recorded in each patient varied from 100.6 F. to 107.2 F., the average of the peak temperatures in primary and recurrent P. vivax malaria was 102.8 F. and 101.4 F., respectively. Typically, complaints of feeling cold gave way to complaints of feeling hot. Cyanosis was replaced by flushing of the skin, and the surface of the entire body felt hot and dry. The pulse was rapid, full and frequently irregular. Vomiting, which began in the cold stage in some of the patients, occurred in and continued throughout most of the hot stage in 43.7 per cent of the patients. Headache, cough, abdominal pain, aching pain in the joints and muscles of the extremities and back were likewise prominent features. Symptoms referable to the central nervous system were not so common in P. vivax as in P. falciparum malaria. Convulsions occurred in 17 patients (5.1 per cent) and delirium and stupor in 9 (2.7 per cent). Fretfulness, irritability and restlessness were recorded in 9 (2.7 per cent), and drowsiness and listlessness in 2 (0.6 per cent). Of the 17 children with convulsions 5 had helminthiasis, pneumonia or dysentery. Although the convulsions might have been caused by either the malarial infection or by the associated unrelated disease, the available evidence favored the former origin. The hot stage lasted from one to eight hours; the usual duration was three to four hours.

Sweating Stage.—During this stage, the temperature fell to normal or below normal. As it began to decline, profuse perspiration broke

out on the forehead and hands followed shortly by sweating of the upper extremities, trunk and lower extremities. At times perspiration was so intense as to saturate the bed clothes. The pulse became slower, symptoms disappeared and many patients fell asleep. When they awakened, several hours later, they seemed to feel well except for a mild degree of exhaustion. The sweating stage lasted for two to three hours; the entire paroxysm occupied from eight to twelve hours.

Symptoms referable to the gastrointestinal tract were common. A history of anorexia, vomiting and diarrhea dating back from one to six days prior to admission to the hospital was frequent, particularly in patients under 3 years of age. Abdominal pain and vomiting were most pronounced during the cold and hot stages. Diarrhea was present in 18, or 5.4 per cent of the patients, 16 of whom were under 3 years of age. In nearly all instances diarrhea was associated with vomiting and varying degrees of dehydration. Generally, the gastrointestinal symptoms disappeared as soon as the malarial infections were brought under control.

The diagnosis of P. vivax malaria was established and treatment started for most of the patients shortly after their admission to the hospital, so that there was little opportunity to observe the course of the temperature in untreated patients. While typical paroxysms occupied from eight to twelve hours and recurred at intervals of forty-eight hours, there was a small number of patients in whom daily paroxysms were observed. These may have been due to infection with two generations of P. vivax, segmenting at different times.

PHYSICAL FINDINGS

Abnormal physical signs were not numerous. Delirium, stupor and sweats have been described under symptoms. Coma was rarely observed. The most important physical findings were in connection with the liver

TABLE 5.—*Physical Findings in P. Vivax Malaria*

	Type of Malaria							
	Primary		Questionable Primary		Recurrent		Questionable Recurrent	
Physical Findings	No.	%	No.	%	No.	%	No.	%
Liver and spleen not palpable..	124	100.0	36	94.7	20	29.8	25	23.8
Spleen palpable.....	0	0.0	0	0.0	41	61.2	61	58.1
Liver palpable.....	0	0.0	2	5.3	3	4.5	6	5.7
Liver and spleen palpable.....	0	0.0	0	0.0	3	4.5	13	12.4

and spleen (table 5). The spleen was not palpable below the costal margin in any of the patients with primary P. vivax malaria, and it was palpable in only 2 patients with questionable primary P. vivax malaria. Although this organ was not palpable, a number of patients had varying amounts of tenderness in the region of the spleen. The spleen was

palpable in 65.7 per cent of the patients with recurrent malaria. The liver alone was palpable in 4.5 per cent. In 29.8 per cent of the patients with recurrent malaria neither liver nor spleen was palpable. When palpable, these organs were usually firm. The lower edge of the liver extended from 1 to 2 cm. below the right costal margin. The lower pole of the spleen extended from 1 cm. below the left costal margin to the level of the umbilicus. Marked splenic enlargement, with the spleen extending to the crest of the ileum, was not observed in P. vivax malaria. The most pronounced splenomegaly was observed in infants and children under the age of 2 years. Abdominal enlargement was usually associated with the splenomegaly and hepatomegaly, although the burden of worms harbored by many of these patients may have contributed to the enlargement.

In evaluating the weights of these children, the normal weights given by Griffith and Mitchell [4] were used as standards. Any weight within plus or minus 7 per cent of these weights was considered within the

TABLE 6.—*Nutritional State of Children with P. Vivax Malaria*

State of Nutrition	Primary		Questionable Primary		Recurrent		Questionable Recurrent	
	No.	%	No.	%	No.	%	No.	%
Poor	9	7.3	7	18.4	17	25.4	34	32.4
Fair	21	16.9	4	10.5	15	22.4	27	25.7
Good	94	75.8	27	71.0	35	52.2	44	41.9

normal range. Children whose weights were 7 to 14 per cent below normal were considered as being fairly well nourished, and those whose weights were more than 14 per cent below normal were considered as being poorly nourished. The heights and other measurements were not known, as these figures were not obtained routinely in the pediatric service. Nutrition was not seriously affected by primary P. vivax malaria, since only 7.3 per cent of the children with this infection were poorly nourished, 16.9 per cent were fairly well nourished and 75.8 per cent were well nourished (table 6). Nutrition seemed to be more seriously affected by recurrent malaria, since 25.4 per cent of the children with this infection were poorly nourished, 22.4 per cent were fairly well nourished and 52.2 per cent were well nourished.

LABORATORY DATA

Hemoglobin Determinations.—Estimations made by the Tallqvist technic were available for the entire group of 334 patients. When the concentration of hemoglobin was found to be below 50 per cent, the

4. Griffith, J. P. C., and Mitchell, A. G.: Textbook of Pediatrics, ed. 3, Philadelphia, W. B. Saunders Company, 1941, pp. 4-5.

result was checked by the Sahli method. The values obtained are given in tables 7 and 8. The average concentration of hemoglobin was 63 per cent. This compared favorably with the average observed in a group of children admitted to the surgical service with simple uncomplicated fractures and free from medical disease. One hundred and twenty (35.9 per cent) had hemoglobin levels of 60 per cent or less and in 67

TABLE 7.—*Average Erythrocyte, Leukocyte and Differential Counts; Concentrations of Hemoglobin and Number of Days Parasites Persisted in Children with P. Vivax Malaria*

Type of Malaria	Primary	Questionable Primary	Recurrent	Questionable Recurrent	General Average
Hemoglobin, per cent.....	64	64	65	60	63
Erythrocytes, million.....	3.6	3.6	3.7	3.5	3.5
Leukocytes, thousand.....	7.1	8.5	7.7	8.0	8.0
Neutrophils, per cent.....	58	62	60	57	59
Lymphocytes, per cent.....	41	37	38	41	40
Eosinophils, per cent.....	1	0.9	3.0	2.0	1.5
Persistence of parasites, days...	2	2.5	2.2	2.2	2..1

of these (20.1 per cent of the total number) levels were below 50 per cent. Low concentrations were observed usually in patients who had experienced several paroxysms at home, before entrance into the hospital, and in patients with questionable recurrent P. vivax malaria. Although 117 patients were infected with intestinal helminths, only 8 of those with concentrations of hemoglobin below 50 per cent had such infections. Thus helminthiasis was not an important factor in the causation of anemia.

TABLE 8.—*Concentration of Hemoglobin in Children with P. Vivax Malaria*

Percentage Hemoglobin	Percentage of Patients			
Type of Malaria	Primary	Questionable Primary	Recurrent	Questionable Recurrent
10	0.8	0.0	0.0	0.0
20	0.0	0.0	0.0	1.0
30	0.8	0.0	0.0	1.9
40	1.6	0.0	0.0	5.7
50	6.5	7.9	4.5	11.4
60	25.0	28.9	35.8	37.1
70	50.0	52.6	47.8	37.1
80	15.3	10.5	11.9	5.7

Erythrocyte Counts.—The patients with erythrocyte counts below 3,200,000 were essentially the same 120 already mentioned as having low hemoglobin values. Counts of less than 2,000,000 were recorded in 4 patients, 3 of whom had only P. vivax malaria and 1 of whom had ascariasis as well as malaria. None of the patients with severe anemia had jaundice.

Leukocyte Counts.—Although the total number of leukocytes varied from 2,200 to 27,300, the average number was 8,000 (table 7). A total of 198, or 59.3 per cent, had counts below this average. Leukocyte counts above 12,000 were obtained in 30, or 9 per cent, of the patients. One of the latter had paratyphoid, 14 had helminthiasis, and 15 had only P. vivax malaria.

Differential Leukocyte Counts.—The number of neutrophils varied from a low of 18 per cent to a high of 90 per cent, with an average of 59 per cent. The number of lymphocytes and monocytes combined varied from 10 to 74 per cent, with an average of 40 per cent (table 7). Although the average number of mononuclear leukocytes was 1.1 per cent, 12 patients had counts of over 5 per cent, and 3 of these had counts between 10 and 14 per cent. The number of basophils was insignificant. The number of eosinophils varied from none to 33 per cent. Twenty-two, or 6.6 per cent of the patients, had eosinophilia with counts of over 4 per cent. Of the 22 who showed this condition, 17 had helminthiasis.

Kahn and Wassermann Tests.—Kahn tests were made on 269 patients. These tests were made after a good response to antimalarial therapy had been obtained. Positive reactions were obtained in 13, or 3.9 per cent, of those tested. Wassermann tests made on this small group of positive reactors gave positive reactions in 12 instances. There was no evidence of coincidental syphilis in any of these patients.

Urinary Examinations.—The urine of 22, or 6.6 per cent of the patients, contained albumin and granular casts. These findings usually disappeared by the time the patients recovered from malaria.

Laboratory Diagnosis of P. Vivax Malaria.—Separate thick and thin films were made on each patient, as described in another report.[2] P. vivax was demonstrated in the peripheral blood of all the patients studied. The following features are characteristic of infection with P. vivax: (1) The young trophozoites appear as signet ring forms one-third the size of the infected erythrocyte, while older ring forms are larger, occupy larger portions of the erythrocytes and exhibit pseudopodial processes indicative of ameboid movement; (2) the infected erythrocytes are pale, become progressively enlarged with increase in the size of the trophozoites; (3) eosinophilic granules (Schüffner's granules) when present appear throughout the portion of the infected cell not occupied by the parasite; (4) young trophozoites contain no pigment, while growing parasites contain yellowish brown pigment granules; (5) the sporulating schizont resembles an irregular grapelike cluster, almost filling the enlarged erythrocyte; (6) the number of merozoites may vary from 12 to 24, with 16 as the usual number; (7) all stages of development of the parasite are present in the peripheral blood, and (8) gametocytes are spherical in shape, the mature microgametocyte being about the size of

a normal erythrocyte and the macrogametocyte usually filling or nearly filling an enlarged erythrocyte. Thus, the diagnosis of P. vivax malaria was based on finding various stages of development of the parasite in the peripheral blood, enlargement of infected erythrocytes, pigmentation of the parasites, and the presence of Schüffner's dots in the parasitized erythrocytes.

Parasites persisted for from one to seven days, with a median of two and an average of two and one-tenth days (table 7). The average in primary malaria was two days, and in recurrent malaria two and two-tenths days (table 7). Gametocytes were observed in 7 patients, 4 of whom had primary and 3 recurrent malaria. When present, gametocytes persisted for from one to four days. Smears were made daily. No patient was discharged from the hospital until three successive negative smears were obtained.

RELAPSES IN P. VIVAX MALARIA

Periods of renewed activity occurred in 67, or 20.1 per cent, of the patients. Eighteen had recrudescences within a period of two months; 23 had relapses within periods of from two to six months and 26 had recurrences within periods of from six to twelve months of the preceding attack. The average interval between periods of renewed activity was slightly more than six months, the distribution having been as follows:

Months Between Periods of Renewed Activity	Number of Patients
1	10
2	8
3	8
4	7
5	3
6	5
7	0
8	3
9	1
10	0
11	1
12	21

The total number of attacks experienced by this group of 67 patients was one hundred and ninety-nine, an average of slightly less than three per child. Thirty patients had two attacks, 15 had three, 17 had four, 4 had five and 1 had six. Thirteen were white children, 9 of whom lived in sanitated areas in the Canal Zone and had acquired their primary infections after single trips into unsanitated areas. The remaining 54 patients lived in large cities of the Republic of Panama or in unsanitated areas. Thus, what was called a relapse or period of renewed activity for purposes of this report may have been a reinfection. The final differentiation between reinfection and relapse could not be made because most of these patients were exposed to infection continually. Of importance in

this connection are the observations of Clark and Komp [5] on malaria in Panama. These investigators conducted blood parasite surveys over a ten year period in a number of villages from which many of the patients in this survey came. They concluded that the large number of infections which they observed were relapses and not reinfections.

Although periods of renewed activity often follow conditions which lower the general resistance of the body, no obvious causes were found in 37 patients. One patient was admitted to the hospital with bilateral suppurative otitis media; P. vivax was demonstrated in his peripheral blood seven days after his entry into the hospital. Another child was admitted with an attack of asthmatic bronchitis; parasites were demonstrated in his blood four days later. The remaining 28 patients were infected with intestinal parasites.

Latent Malaria.—Children with persistent malarial infections are encountered frequently in numerous regions on the Isthmus of Panama. Among 2,939 infected children, Clark and Komp [5] observed that 405 were infected with P. vivax alone and that 297 were infected with P. vivax in addition to other species of malarial parasites. Thus, 23.9 per cent were infected with P. vivax. This type of infection is known as latent infection. The general impression is that latent malaria is a parasitemia without serious clinical manifestations. Latent malaria is not malaria without serious clinical manifestations. If children with latent P. vivax infections were observed over extended periods of time, it would be seen that during periods of renewed activity their infections do not differ from those observed in hospitals. Such children are carriers of malaria and are a danger to other members of the community. They are the inhabitants of the unsanitated areas in the Canal Zone and interior of the Republic of Panama.

COMPLICATIONS OF P. VIVAX MALARIA

Complications were observed infrequently in the 334 patients with P. vivax malaria. Acute suppurative otitis media occurred in 4 patients and bronchopneumonia in 3. One child had bronchopneumonia when he was admitted to the hospital. In 3 patients it developed on the seventh and twelfth days following their admission to the hospital. There was no reason to believe that the pneumonia in these patients was caused by P. vivax. Albuminuria was observed in 6.6 per cent of the patients. It disappeared by the time the patients recovered from malaria. A 7 year old boy, who had acute glomerulonephritis when he was admitted to the

5. Clark, H. C., and Komp, W. H. W.: A Summary of Ten Years of Observation on Malaria in Panama with Reference to Control with Quinine, Atabrine and Plasmochin, Without Antimosquito Measures, in Moulton, F. R.: A Symposium on Human Malaria, Publication 15, American Association for the Advancement of Science, Washington, D. C., 1941, pp. 273-284.

hospital, recovered in six weeks. From one to four convulsions occurred in 17 patients. Delirium, stupor and coma were observed infrequently. As nearly as could be determined, there were no residual effects from these symptoms. Severe anemia with concentrations of hemoglobin below 50 per cent was observed in 20.1 per cent of the patients. There was considerable decrease in size of the enlarged spleens at the termination of antimalarial therapy. In some of the patients in whom only moderate splenic enlargement was present, the spleen was not palpable when the patients were discharged from the hospital.

The most frequent associated unrelated condition encountered with P. vivax malaria was intestinal helminthiasis. Four children had diseases of the respiratory tract; 2 had acute communicable diseases; 1 had dysentery and 1 had paratyphoid. Tuberculin tests were made on 227 of the 334 patients, and positive reactions were obtained in 30. One child had roentgen evidence of the childhood type of tuberculosis.

PROGNOSIS OF P. VIVAX MALARIA

There were no deaths in this group of 334 patients. The patients who had associated unrelated diseases in addition to P. vivax malaria on admission to the hospital seemed to do as well as those without associated disease. Recently a 4 year old girl, not included in this study, was admitted to the hospital with acute anterior poliomyelitis and involvement of the lower extremities. She was poorly nourished and weighed 22 pounds (10 Kg.). The spleen was firm and extended to the umbilicus. The hemoglobin was 40 per cent; there were 2,100,000 erythrocytes per cubic millimeter of blood and 12,400 leukocytes, with 67 per cent neutrophils, 27 per cent lymphocytes and 6 per cent eosinophils. P. vivax organisms were demonstrated in thick and thin blood smears. In addition, she had a massive infection with A. lumbricoides and passed over 400 ascarides after appropriate anthelmintic therapy. Aside from the usual residuals of poliomyelitis, this child recovered uneventfully.

In Canal Zone hospitals, all forms of malaria are considered serious infections. An attempt is made to establish an early diagnosis and to institute therapy as soon as possible after the diagnosis has been established. These factors, coupled with the fact that P. vivax malaria is usually a benign infection, may have accounted for the absence of deaths in this group of patients.

TREATMENT

The drugs used in the treatment of P. vivax malaria were quinine, quinacrine hydrochloride and pamaquine naphthoate. The preparations used, dosages and modes of administration were the same as those employed in the treatment of P. falciparum malaria and have been discussed in another report.[2]

Treatment with Quinine.—Quinine was administered to 33 patients (table 9). Quinine dihydrochloride was administered intramuscularly to 3 of these patients. It was not administered intravenously to any of the patients in this study. Parasites disappeared from the peripheral blood in 31 of the 33 patients in from one to six days, with an average of two and one-tenth days. In 2, or 6 per cent, gametocytes developed after one week of therapy with quinine. In figure 2 may be seen the average temperature curve of all of the quinine-treated patients with primary and recurrent P. vivax malaria. This average temperature curve has been compared with similar curves established for the patients treated with quinacrine hydrochloride. No important differences between the response of fever to quinine or quinacrine hydrochloride in primary or recurrent P. vivax malaria were observed.

Toxic effects from quinine were uncommon, although older children occasionally complained of ringing in their ears. Vomiting occurred

TABLE 9.—*Drugs Employed in the Treatment of P. Vivax Malaria*

Drug	Type of Malaria				
	Primary	Questionable Primary	Recurrent	Questionable Recurrent	Total No. of Cases
Quinacrine hydrochloride	111	35	54	95	295
Quinine	11	2	13	5	31
Quinacrine hydrochloride and quinine	1	0	0	1	2
Quinacrine hydrochloride and pamaquine naphthoate	1	0	0	3	4
Quinine and pamaquine naphthoate	0	1	0	1	2

frequently. Usually this symptom was present on admission to the hospital. Even though it continued for a variable period of time, it could not be determined with finality whether this symptom was either caused or aggravated by quinine.

Treatment with Quinacrine Hydrochloride.—Quinacrine hydrochloride was administered to 301 patients (table 9). Because of severe vomiting, delirium or stupor peroral treatment was not feasible in 72 patients. In these patients from one to three doses of quinacrine hydrochloride were administered intramuscularly without noticeable toxic effect. Although areas of induration occasionally occurred at the sites of injections, formation of abscesses was not observed. Parasites disappeared from the peripheral blood in from one to seven days in 295 of the 301 patients, with an average of two and two-tenths days. In 2 patients trophozoites persisted throughout seven days of treatment with quinacrine hydrochloride, necessitating a change to quinine. In 4, or 1.3 per cent, of the patients treated with quinacrine hydrochloride gametocytes developed. In figure 2 may be seen the average temperature curve of all the patients with primary and recurrent P. vivax

malaria who were treated with quinacrine hydrochloride. This average temperature curve has been contrasted with similar curves established for the quinine-treated patients. No important differences between the response of fever to quinacrine hydrochloride or quinine in primary or recurrent P. vivax malaria were observed.

Toxic effects due to quinacrine hydrochloride were not observed. A yellow discoloration of the skin and scleras developed on the third

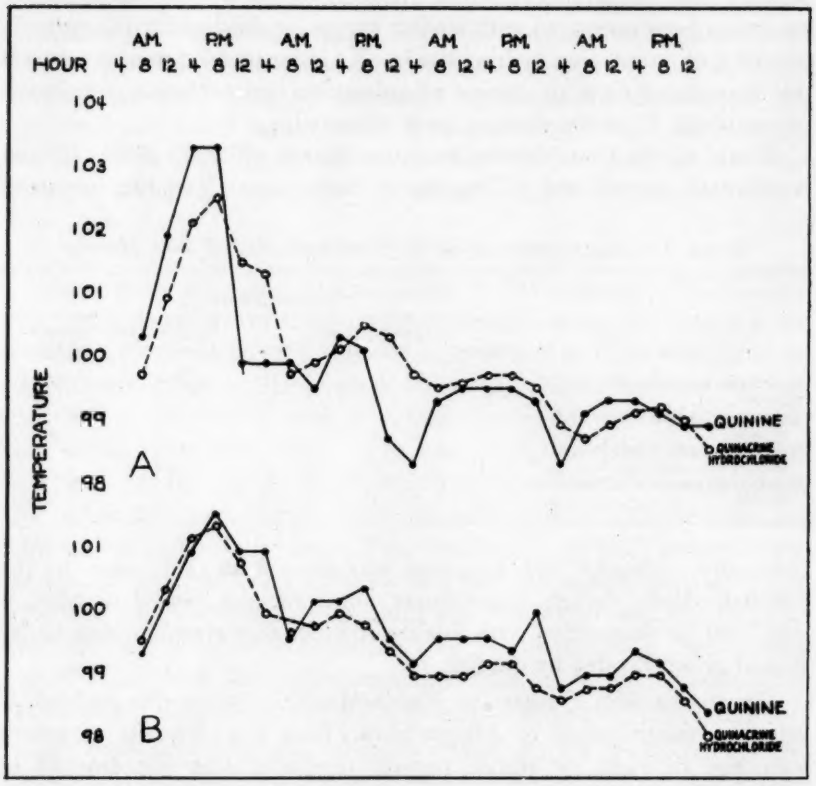


Fig. 2.—Response of the temperature of patients with malaria to therapy. The solid line represents the average temperature curve of the patients treated with quinine and the broken line the average temperature curve of the patients treated with quinacrine hydrochloride. *A*, Response of the temperature in primary P. vivax malaria to therapy. *B*, Response of the temperature in recurrent P. vivax malaria to therapy.

to the fifth day of treatment in most of the patients. This was interpreted as being due to a deposition of the drug in the tissues and as a harmless rather than a toxic symptom. In no instance was the use of quinacrine hydrochloride discontinued because of discoloration of the skin.

Pamaquine Naphthoate.—This drug was administered to the 6 patients who showed gametocytes in the peripheral blood after treatment with quinine or quinacrine hydrochloride (table 9). It was not used alone in the treatment of the acute attacks of P. vivax malaria. Gametocytes persisted from two to five days after therapy with pamaquine naphthoate was instituted. Toxic effects were not observed in the 6 children treated with pamaquine naphthoate.

General Treatment.—Patients were confined to their beds as long as acute symptoms were present. The administration of fluids was urged during the febrile periods. When vomiting, diarrhea and dehydration were present, fluids were administered parenterally as indicated. When necessary, barbiturates were used for sedation; appropriate anthelmintic drugs were administered to those who were infected with intestinal parasites; hematinics and occasionally transfusions of blood were used in the treatment of anemia. The response to hematinics after the malarial infections were controlled and the burdens of worms reduced was excellent in most cases. For 5 children with severe anemias, one or more transfusions of blood were necessary.

QUARTAN MALARIA

Malaria due to infection with Plasmodium malariae was observed in 10 patients as compared with 334 with malaria due to infection with P. vivax and 493 with malaria due to infection with P. falciparum. Thus the ratio of quartan to other types of malaria was 1 to 84. During the period covered by this survey, there were three years in which there was 1 case each year, two years in which there were 2 cases each year and one year in which there were 3 cases.

The pertinent data pertaining to the patients infected with P. malariae are presented in table 10. All the patients were mestizos. Two lived in a large city in the Republic of Panama. One of these children had no history or physical signs suggestive of recurrent malaria, and the source of his infection could not be traced to an unsanitated area. The residence of the second patient had been in an unsanitated area up to four months before her admission to the hospital. Physical signs suggestive of recurrent malaria were present. It was doubtful that the infection for which this patient was admitted to the hospital was a primary infection. It was also doubtful that she had acquired her infection in a sanitated area. The remaining 8 patients lived in unsanitated areas. Four had histories of previous attacks of malaria of unknown type, 5 had negative histories, and 1 had a history of bouts of fever of unknown cause. In only 1 instance, however, could a definite diagnosis of primary malaria be entertained.

Except for the difference in periodicity, the symptoms of quartan malaria were essentially the same as those observed in P. vivax malaria.

TABLE 10.—*Summary of Ten Cases of Quartan Malaria in Children in which Treatment was with Quinacrine Hydrochloride*

Case No.	Sex, Age, Race, Type of Residence	History of Previous Attack of Malaria	Symptoms	Findings in Hospital	Associated Conditions	Clinical Course	Comment
1	M 10 Mestizo R. P.*	None	Fever every 3d day for 1 week; anorexia	Weight 64 lb. (29 Kg.); hemoglobin 60%, erythrocytes 3,200,000, leukocytes 4,700	None	Temperature 98 to 102 F. first day and normal thereafter; parasites in peripheral blood 3 days	Primary malaria; origin of infection could not be traced to unsanitated area
2	M 7 Mestizo Unsanitated	None	Chills and fever; vomiting	Weight 46 lb. (20.9 Kg.); hemoglobin 75%, erythrocytes 3,800,000, leukocytes 7,600	None	Temperature 98.2 to 104.8 F. first day and normal thereafter; vomiting persisted 1 day; parasites in peripheral blood 2 days	Questionable primary malaria; first 3 doses of quinacrine hydrochloride administered intramuscularly
3	F 6 Mestizo Unsanitated	Attack of unknown type 7 mo. prior to present admission	Fever; headache; vomiting	Weight 38 lb. (17.2 Kg.); spleen 4 cm. below costal margin; abdomen protuberant; hemoglobin 50%, erythrocytes 2,700,000, leukocytes 11,000, neutrophils 72%, lymphocytes 22%, eosinophils 6%	Ascariasis	Temperature 98 to 100.2 F. throughout illness; parasites in peripheral blood 4 days	Recurrent malaria; patient ill 15 days before admission; hospitalized 20 days; spleen not palpable; hemoglobin 62%; no ova in stool when patient discharged
4	M 2 Mestizo Unsanitated	Attack of unknown type 8 mo. prior to present admission	Fever; anorexia	Weight 21 lb. (9.5 Kg.); infected burns on hands and face; hemoglobin 45%, erythrocytes 2,500,000 leukocytes 5,500	Creosote burns on hands and face incurred 11 days prior to admission	Temperature 98 to 104.2 F. for 3 days and normal thereafter; parasites in peripheral blood 2 days	Recurrent malaria; provocative cause present; temperature became normal when infection of burns was brought under control
5	M 6 Mestizo Unsanitated	Attack of unknown type 4 mo. prior to present admission	Chills and fever every 3d day for 2 weeks; anorexia	Weight 34 lb. (15.4 Kg.); spleen 3 cm. below costal margin; hemoglobin 40%, erythrocytes 2,100,000, leukocytes 6,400	Ancylostomiasis	Temperature normal except on 3d day, when it ranged from 100 to 104.2 F.; parasites in peripheral blood 3 days	Recurrent malaria; chill and fever 3d day in hospital; hemoglobin 55%, no ova in stool when patient discharged 14 days after admission

6	F 8 Mestizo R. P.*	None	Chills and fever; headache; anorexia; malaise	Weight 57 lb. (25.9 Kg.); spleen 1 cm. below costal margin; hemoglobin 60%, erythrocytes 3,700,000 leukocytes 5,200	Strongyloidiasis	Temperature 100 to 103 F. first day and normal thereafter; parasites in peripheral blood 2 days	Questionable recurrent malaria; residence in unsanitated district 4 mo. prior to present admission
7	M 6 Mestizo Unsanitated	None	Chills and fever; abdominal pain; cough; vomiting	Weight 34 lb. (15.4 Kg.); spleen 3 cm. below costal margin; hemoglobin 58%, erythrocytes 3,200,000, leukocytes 9,600, neutrophils 49%, lymphocytes 44%, eosinophils 7%	Ascariasis; trichuriasis	Temperature 98 to 100.4 F. throughout illness; parasites in peripheral blood 2 days	Questionable recurrent malaria; spleen not palpable and ova of T. trichiura in stool when patient was discharged from hospital
8	M 8 Mestizo Unsanitated	Attack of unknown type 3 mo. prior to present admission	Anorexia; fever; generalized aches	Weight 42 lb. (19.1 Kg.); spleen 2 cm. below costal margin; hemoglobin 60% erythrocytes 3,200,000, leukocytes 3,200	Ascariasis; trichuriasis	Temperature 97.6 to 101.4 F. first day, and normal thereafter; parasites in peripheral blood 2 days	Questionable recurrent malaria; ova of T. trichiura in stool when patient was discharged from hospital
9	F 7 Mestizo Unsanitated	None	3 bouts of chills and fever at intervals of 3 days; cough	Weight 37 lb. (16.8 Kg.); spleen 2 cm. below costal margin; hemoglobin 50%, erythrocytes 2,600,000, leukocytes 4,800	None	Temperature normal except on 2d day when it ranged from 98.4 to 104.2 F.; parasites in peripheral blood 2 days	Questionable recurrent malaria; chill and fever 2d day in hospital
10	F 12 Mestizo Unsanitated	Bouts of fever of unknown cause	Chills and fever; vomiting	Weight 60 lb. (27.2 Kg.); spleen 2 cm. below costal margin; hemoglobin 55%, erythrocytes 3,000,000, leukocytes 4,700	Oxyuriasis	Temperature normal except on 3d day when it ranged from 99.8 to 102 F.; parasites in peripheral blood 3 days	Questionable recurrent malaria; chill and fever 3d day in hospital

* Principal city in the Republic of Panama.

The small number of patients made further analysis of little value. Delirium, stupor, coma and convulsions were not observed. Typical paroxysms lasting four to eight hours and consisting of chill, fever and sweating were observed in 4 patients. One child had fever daily for three days which may have been due to infection with more than one generation of parasites, which sporulated at different times. However, infected burns on his hands and face seemed to offer a more obvious explanation for the elevations of temperature which occurred. Anemia and subnormal weight were frequent, although the role of quartan malaria in their production could not be evaluated.

Quinacrine hydrochloride was used in the treatment of all of the patients. Because of the presence of severe vomiting, 1 patient was given three intramuscular injections of the drug. Three patients had typical paroxysms from one to three days after therapy was instituted. In 6 patients, the temperature became normal two or three days after therapy was started. One patient had a temperature which ranged from 98 F. to 100.2 F. daily for twenty days. No tenable explanation for this persistent elevation was found.

For only 3 children was there obtained a history of chills and fever recurring at intervals of seventy-two hours, suggesting infection with P. malariae. Quartan malaria was diagnosed by demonstrating P. malariae in thick and thin blood smears. The following features are characteristic of infection with P. malariae: (1) Ring forms of the parasite are about the size of those of P. vivax, while mature schizonts almost fill the infected erythrocytes; (2) the infected erythrocytes are neither enlarged nor distorted, and multiple infection of erythrocytes is uncommon; (3) the parasites are heavily pigmented; (4) there is no stippling of infected erythrocytes and Schüffner's dots are absent; (5) the number of merozoites varies from six to twelve; (6) all stages of development of the parasite are present in the peripheral blood, and (7) gametocytes are spherical in shape.

MIXED INFECTIONS

There were 8 patients in whom two or more species of parasites were present simultaneously. The pertinent data pertaining to these patients are presented in table 11. Seven were infected with two species of parasites and 1 was infected with three. The combinations of infections in these patients were as follows:

Combination of Parasites	No. of Patients
P. falciparum and P. vivax	3
P. falciparum and P. malariae	2
P. malariae and P. vivax	2
P. falciparum, P.. malariae and P. vivax	1

All the patients lived in unsanitated areas, and 6 had histories of previous attacks of malaria within a period of one year. Two had

been treated previously for quartan malaria and 1 for P. falciparum malaria. Evidences of recurrent malaria were present in the 2 patients who had no histories of previous attacks of malaria.

The manifestations of malaria due to mixed infections resembled those observed in the cerebral and algid forms of P. falciparum malaria. The only exceptions were possibly the 2 cases of mixed infections of P. malariae and P. vivax. However, there was no doubt that the symptoms manifested by these 2 patients were more severe than the symptoms observed in the average case of either P. vivax or quartan malaria. Four patients were brought to the hospital within twenty-four hours and 4 were admitted three, five, eight and ten days after the onset of symptoms. Delirium was present in 3 patients, coma in 2, convulsions in 1 and muscular twitchings in 1. Two patients vomited, and 3 had diarrhea. Although temperatures over 106 F. were not observed, the average duration of temperature above 101 F. was slightly more than three days. Subnormal weight, splenomegaly and anemia were common. Five patients had intestinal helminthiasis. The child who had P. falciparum, quartan and P. vivax malaria also had ancylostomiasis, ascariasis, strongyloidiasis and trichuriasis. The average persistance of parasites in the peripheral blood was slightly more than six days as compared with two and two-tenths days in P. falciparum malaria and two and one-tenth days in P. vivax malaria. P. falciparum gametocytes were observed in 3 patients.

One patient was treated with quinine. Another patient was treated with quinacrine hydrochloride for seven days, quinine for six days and pamaquine naphthoate for five days. Six patients were treated with quinacrine hydrochloride. Two of the latter showed gametocytes and received pamaquine naphthoate at the termination of therapy with quinacrine hydrochloride. In 2 patients the first few doses of quinacrine hydrochloride were administered intramuscularly. In 1 of these patients an area of necrosis developed at the site of an injection. Otherwise, no toxic symptoms were observed from either quinine or quinacrine hydrochloride. The administration of fluids intravenously and intramuscularly to 4 patients who had severe cerebral or gastrointestinal manifestations was of importance second only to the administration of the drug.

COMMENT

Pediatricians usually attempt to find a single diagnosis which will emcompass all the symptoms and physical signs manifested by a child. Such a practice in the tropics will often lead to embarrassing situations and occasionally to disastrous results. Two things are learned quickly: (1) that children in the tropics have the same anomalies, diseases and infections encountered in more temperature zones and (2) that these conditions commonly occur in association with infections peculiar to

TABLE 11.—*Summary of Eight Cases of Malaria Due to Mixed Infections*

Case No.	Sex, Age, Race, Type of Residence	History of Previous Attack of Malaria	Symptoms	Findings in Hospital	Associated Conditions	Clinical Course	Therapy	Comment
1	M 6 Mestizo Unsanitated	Attack of unknown type 8 mo. prior to present admission	Chills and fever daily for 3 successive days; abdominal pain; vomiting; diarrhea	P. vivax and P. falciparum; weight 40 lb. (18.1 Kg.); spleen 1 cm. below costal margin; hemoglobin 60%, erythrocytes 3,700,000, leukocytes 8,000	None	Temperature 99.6 to 106 F. first day, 99 to 101 F. third day and normal remaining time; marked delirium first day; parasites in peripheral blood 3 days	3 doses of quinine intravenously in isotonic solution of three chlorides, followed by quinine orally for 6 days	Seriously ill for 24 hr. no toxic reactions from intravenous use of quinine
2	M 9 Mestizo Unsanitated	Attack of unknown type 4 mo. prior to present admission	Chills and fever; anorexia	P. vivax and P. falciparum; weight 44 lb. (20 Kg.); spleen 3 cm. below costal margin; hemoglobin 55%, erythrocytes 2,500,000, leukocytes 6,300, eosinophils 5%	Strongyloidiasis	Temperature 99.6 to 104.4 F. for 2 days and normal thereafter; parasites in peripheral blood 2 days	Quinacrine hydrochloride	Ill 10 days prior to admission to hospital; spleen not palpable; hemoglobin 60%; larvae of S. stercoralis in stool when discharged
3	M 8 Mestizo Unsanitated	Attack of unknown type 11 mo. prior to present admission	Chills and fever; cough	P. vivax and P. falciparum; weight 47 lb. (21.3 Kg.); spleen 2 cm. below costal margin; hemoglobin 65%, erythrocytes 3,400,000, leukocytes 8,700	Ascariasis	Temperature 98.4 to 105.2 F. for 2 days and normal thereafter; delirium first day; parasites in peripheral blood 4 days	Quinacrine hydrochloride; fluids intravenously	Ill 5 days prior to admission to hospital; spleen not palpable; no ova in stool when discharged
4	M 19 mo. Mestizo Unsanitated	None	Fever; anorexia; vomiting; diarrhea; convulsions	P. falciparum and P. malariae; weight 18 lb. (8.2 Kg.); spleen 2 cm. below costal margin; hemoglobin 65%, erythrocytes 3,400,000, leukocytes 8,700	None	Temperature 98.2 to 106 F. for 3 days, 98 to 101 F. for 2 days and normal thereafter; trophozoites in peripheral blood 6 days; P. falciparum gametocytes 3 days	3 doses of quinacrine hydrochloride intramuscularly followed by quinacrine hydrochloride orally; fluids given intravenously and subcutaneously; pamaquine naphthoate	Questionable recurrent malaria; critically ill 3 days; coma but no convulsions; diarrhea and dehydration pronounced

5	F 7 Mestizo Unsanitated	Attack of P. falciparum malaria 5 mo. prior to present admission	Chills and fever; weakness	P. falciparum and P. malariae; weight 31 lb. (14.1 Kg.); spleen 4 cm. below costal margin; hemoglobin 50%, erythrocytes 2,900,000, leukocytes 8,800	None	Temperature 99.2 to 105.4 F. for 2 days and normal thereafter; trophozoites in peripheral blood 3 days, P. falciparum gametocytes 9 days	Quinacrine hydrochloride; pamaquine naphthoate	Ill 8 days prior to admission; first attack of malaria due to infection with P. falciparum; spleen not palpable when discharged from hospital
6	F 18 mo. Mestizo Unsanitated	None	Fever; cough; diarrhea	P. malariae and P. vivax; weight 18 lb. (8.2 Kg.); spleen 2 cm. below costal margin; hemoglobin 60%, erythrocytes 3,500,000, leukocytes 5,800	Trichuriasis	Temperature 99 to 104.8 F. for 2 days and normal thereafter; parasites in peripheral blood 2 days	Quinacrine hydrochloride	Questionable recurrent malaria; spleen not palpable; ova of T. trichiura in stool when discharged from hospital
7	M 11 Mestizo Unsanitated	Attack of quartan malaria 3 mo. prior to present admission	Fever; cough	P. malariae and P. vivax; weight 75 lb. (34 Kg.); spleen 2 cm. below costal margin; hemoglobin 60%, erythrocytes 3,200,000, leukocytes 5,400	Oxyuriasis	Temperature 98.6 to 104 F. for 3 days and normal thereafter; parasites in peripheral blood 5 days	Quinacrine hydrochloride	No definite chills observed; spleen not palpable and no ova of E. vermicularis in stool when discharged from hospital
8	M 6 Mestizo Unsanitated	Attack of quartan malaria 6 mo. prior to present admission	Fever; delirium	P. falciparum, P. malariae and P. vivax; weight 34 lb. (15.4 Kg.); spleen 3 cm. below costal margin; hemoglobin 20%, erythrocytes 1,800,000, leukocytes 10,300, neutrophils 74%, lymphocytes 24%, eosinophils 2%	Ancylostomiasis; ascariasis; strongyloidiasis; trichuriasis	Temperature 99.2 to 106 F. daily; muscular twitching and coma for 6 days; trophozoites in peripheral blood 4 days and P. falciparum gametocytes for 10 days	3 doses of quinacrine hydrochloride intramuscularly followed by quinacrine hydrochloride orally for 6 days, quinine 6 days, pamaquine naphthoate 5 days	Critically ill; cerebral form of malaria; fluids intravenously and/or intramuscularly for 7 days; quinacrine hydrochloride administered by stomach tube for 5 days; necrotic area in left buttock; spleen not palpable; ova of T. trichiura in stool when discharged 57 days after admission

the tropics. Recently a 4 year old mestizo girl, not included in this survey, was admitted to the hospital with a primary attack of P. falciparum malaria of average severity. Although stools were examined on two occasions, no ova were found. She was treated with quinacrine hydrochloride, and parasites disappeared from the peripheral blood on the third day. Her temperature was normal on the fourth day. On the fifth day, the temperature was 102 F., and on the sixth day it was 104 F. A ward physician discontinued administration of the quinacrine hydrochloride and substituted quinine. Moderate abdominal distention developed and the child died on the eighth day. At autopsy no malarial parasites or pigment were found in the internal organs. The child had a generalized peritonitis. Further search revealed the disheartening fact that she had helminthiasis due to infection with a single male ascarid. This parasite had made its way into the peritoneal cavity through a perforation in the appendix. The child recovered from the disease for which she was admitted to the hospital, but died of another disease which had been overlooked completely. Helminthiasis and malaria are commonplace infections in children living in unsanitated areas. Frequently both infections are observed in the same patient. Infections of the respiratory tract, dysentery and injuries are also common, and occasionally these are the provocative factors which precipitate periods of renewed activity of malaria.

Because of the frequency with which patients harbor several infections simultaneously, it is difficult to determine which infection is responsible for producing existing symptoms and physical signs. The greatest difficulties were encountered in connection with the interpretation of such symptoms and signs as convulsions, fever, anemia, subnormal weight and retarded growth. The presence of several infections any one of which could be the responsible factor made it difficult to establish one infection as the predominant cause. Under such circumstances conclusions cannot be final and must of necessity be in the nature of generalizations.

During the period extending from July 1, 1939, to July 1, 1945, 845 children were treated for malaria in hospitals in the Canal Zone. Four hundred and ninety-three cases were due to infection with P. falciparum, 334 were due to infection with P. vivax, 10 were due to infection with P. malariae and 8 were due to mixed infections, a ratio of 62:42:1:1. In some parts of the world tertian malaria is more common than P. falciparum malaria. In the Canal Zone and adjoining areas this was not found to be the case in children during the years covered by this survey. Here P. falciparum malaria was half again as common as P. vivax malaria.

On the Isthmus of Panama breeding of the anopheline vectors of malaria continues throughout the year, although in some localities it is

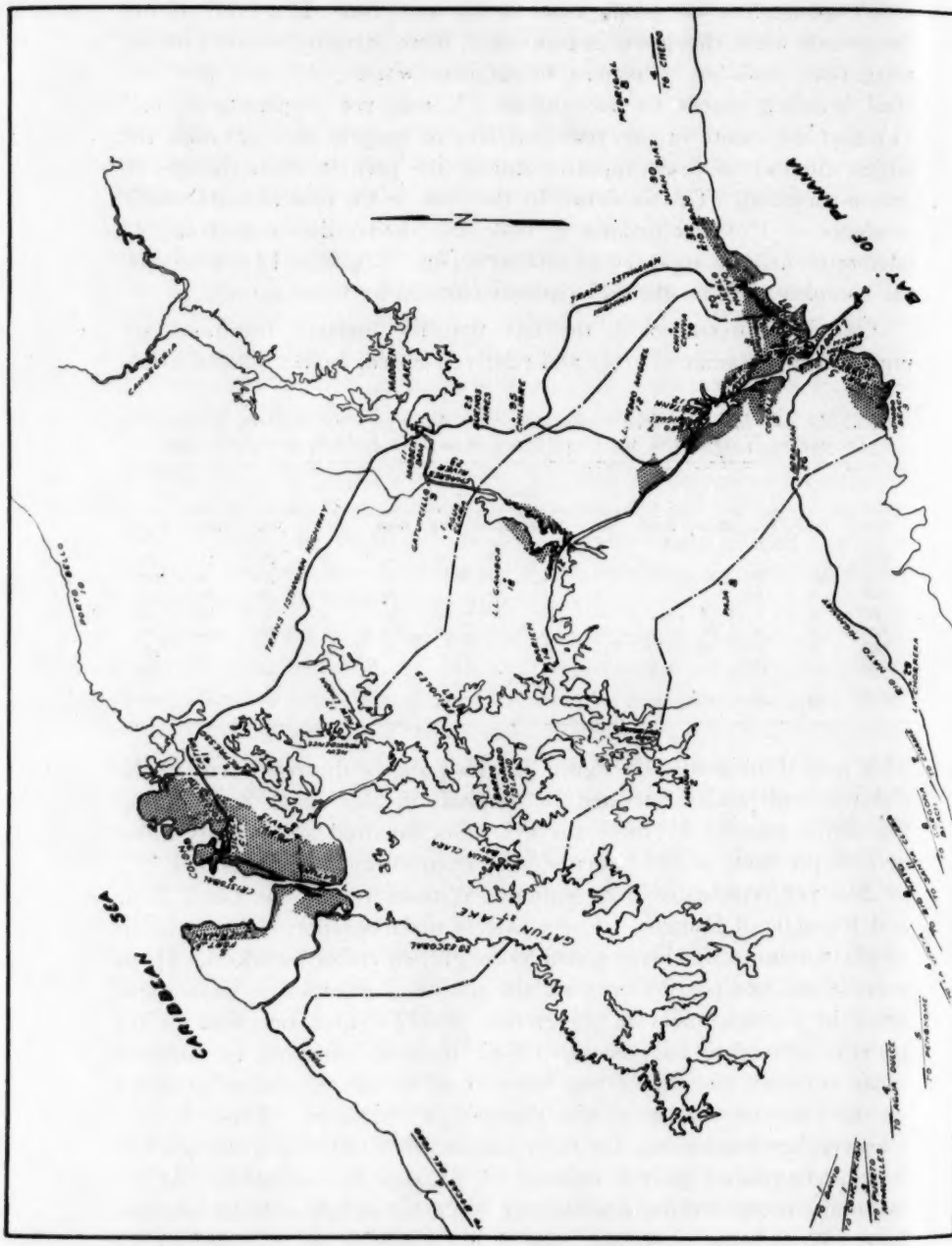
relatively reduced during the height of the dry season. During the rainy season, streams are full, rapid and prone to floods, thus offering little or no opportunity for propagation of the mosquito. However, during the periods when changes of season occur, many streams become nothing more than pools or collections of stagnant water. As such they are ideal breeding places for mosquitoes. It was not surprising to find (1) that no month of the year was free of malaria and (2) that the largest number of cases appeared during the periods when changes of season occurred. This is shown by the data on the monthly and yearly incidence of P. vivax malaria in table 1. Similar data concerning P. falciparum malaria appeared in another report.[2] In table 12 is presented the complete data on the 845 patients covered by these surveys.

One is impressed with the fact that the malarial infections are prevalent in unsanitated areas and relatively absent from sanitated areas.

TABLE 12.—*Monthly and Yearly Incidence of All Types of Malaria in Children Treated in Hospitals in the Canal Zone from July 1, 1939, to July 1, 1945*

	Month												
Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1939	..	..	..	..	..	..	9	5	11	19	19	17	80
1940	23	18	12	12	9	14	21	13	12	11	13	9	167
1941	6	9	7	5	8	11	12	3	10	11	9	20	111
1942	6	9	2	9	23	21	16	10	13	8	6	18	141
1943	8	2	9	5	10	6	12	9	4	7	10	5	87
1944	10	5	10	8	15	15	17	24	18	11	7	16	156
1945	21	17	17	9	22	17	..	..	..	..	..	..	103
Total	74	60	57	48	87	84	87	64	68	67	64	85	845

This is best illustrated in figure 3, which shows the residences of the children with malaria treated in hospitals in the Canal Zone during the period covered by these surveys. Six hundred and seventy-three, or 79.6 per cent, of 845 patients came from unsanitated areas and 172, or 20.4 per cent, came from sanitated communities in the Canal Zone and Republic of Panama. Every case of malaria reported from a sanitated community was investigated thoroughly by trained workers. However, it was not possible to trace the source of infection to unsanitated areas in a single child in this group of 172. That one fifth of the patients seemed to have acquired their malarial infections in sanitated areas not only was disturbing, but seemed to cast a shadow of doubt on the efficiency of the efforts directed at sanitation. These figures, however, are misleading, for there can be no doubt that a miracle has been accomplished on the Isthmus of Panama by sanitation. At the beginning of the century a white man could not escape malarial infection here. Now he is reasonably safe if his activities are confined to the sanitated areas and if he follows the few simple rules laid down for his protection by the health department. Human beings wander about


BAY OF PANAMA
CARIBBEAN SEA
GATUN LAKE
TRANS-ISTHMIAN HIGHWAY
TO COLON
TO PANAMA

considerably. Most of them cannot honestly recall where they have been every hour of the day or night over a period of time corresponding to the incubation period of malaria. When one obtains a history indicating that a child has acquired malaria in a sanitated area, such information must be interpreted in the light of this knowledge of the habits of human beings.

The native villages of Chilibre and Chiva Chiva are districts in which P. vivax malaria is highly endemic. Even though the result of analysis of the areas from which patients treated in local hospitals come indicates the contrary, there are numerous areas which belong in the same category. Chilibre and Chiva Chiva are located on a paved road which provides ready access to hospitals. Water transportation is available to other villages. Many villages, however, are isolated and have neither roads nor water transportation. Patients living in such areas do not reach hospitals in the Canal Zone. The result is that the available data do not reveal the numerous villages which are reservoirs of malarial infection.

Typical paroxysms consisting of chill, fever and sweat occurred no more frequently in P. vivax than in P. falciparum malaria. In all the malarial infections in children the typical paroxysm was usually not observed under the age of 2 years and was infrequently observed under the age of 3 years. The pattern of the paroxysm was irregular, and symptoms characteristic of one stage commonly extended into other phases of the paroxysm. There was no doubt that infection with P. vivax resulted in a milder type of malaria than did infection with P. falciparum. While the malignant cerebral and algid forms were common in the latter, they were practically absent in the former. Although delirium and convulsions were observed in P. vivax malaria, they were not so frequent or so severe as in P. falciparum malaria. The important physical findings observed in P. vivax malaria consisted of signs of anemia, splenomegaly and subnormal weight, although they were not observed as commonly as in P. falciparum malaria. Anemia when not due to associated unrelated diseases depended more on the number of paroxysms experienced by the patient than on whether an attack was primary or recurrent. Infants under the age of 2 years seemed to have the greatest degree of splenomegaly. The triad of splenomegaly, subnormal weight and anemia was relatively common in recurrent P. vivax malaria. The subnormal weight and the anemia may have been attributable in part to infection with intestinal parasites. The cachexia observed in P. falciparum malaria was not a feature of tertian malaria.

Complications and sequelae were uncommon in P. vivax malaria. Althought 3 patients had bronchopneumonia and 4 had acute suppurative otitis media, there was no reason for assuming that P. vivax had an etiologic relationship to these complications. The albuminuria observed

in 6.6 per cent of the patients disappeared by the time the patients recovered from malaria. The anemias observed in one fifth of the patients improved rapidly with hematinics after malarial, helminthic or other infections were either controlled or eliminated. Five patients with severe anemia required one or more transfusions of blood.

There were no deaths among the 334 patients with P. vivax malaria as compared with 12 deaths among the 493 patients with P. falciparum malaria. Thus the strains of P. vivax present on the Isthmus of Panama produced in children treated early and effectively a benign type of infection unassociated with a mortality rate of consequence during the period covered by this survey.

Both quinine and quinacrine hydrochloride were effectively employed in the treatment of the acute attacks of all forms of malaria in children. Toxic reactions from either of these agents were rarely observed. From the point of view of toxicity, there seems to be no choice between them. Both drugs affect all forms of the common species of malarial Plasmodia found in the human being, although quinacrine hydrochloride seems to be more effective in eliminating malarial infection. Quinine probably does not destroy gametocytes, although it acts indirectly by destroying the schizonts from which gametocytes develop. Quinacrine hydrochloride, on the other hand, destroys the gametocytes of P. vivax and P. malariae but is ineffective against the gametocytes of P. falciparum. In so far as the effect on fever is concerned, reference to figure 2 indicates that the return of temperature to normal occurred as quickly in the patients treated with quinacrine hydrochloride as it did in the quinine-treated patients. Either drug, if administration was started during or shortly after the first paroxysm of P. vivax malaria, usually diminished the severity of the second and completely prevented the occurrence of a third. Trophozoites disappeared from the peripheral blood of the patients treated with quinacrine hydrochloride in two and two-tenths days as compared with two and one-tenth days for those treated with quinine. Thus there was no evidence that the response of P. vivax malaria to treatment with quinacrine hydrochloride was slower than the response to quinine. There was no evidence on which to base conclusions regarding the relative frequency of relapses in the two groups of patients.

Obviously, quinacrine hydrochloride and quinine are equally effective in the treatment of the early acute attacks of malaria in children. The determining factor in the efficiency of action seems to depend on the plasma concentration of each of these drugs. Quinine is absorbed rapidly from the gastrointestinal tract; a large percentage is oxidized in the body, and the unoxidized portion is excreted rapidly by the kidneys. Quinacrine hydrochloride is absorbed more slowly than quinine from the gastrointestinal tract; it is excreted slowly, tends to be

cumulative in action and is stored in the liver and the skin. Thus effective plasma levels are attained more rapidly with quinine than with quinacrine hydrochloride. In order to obtain effective levels of quinacrine hydrochloride, early initial doses must be large. Because quinine is oxidized and excreted rapidly effective plasma levels are of short duration. Maximum plasma concentrations of quinine should coincide with release of new generations of merozoites. Administration of this drug should be planned so that maximum concentration is obtained at such times.

SUMMARY

In the Canal Zone and adjoining areas of the Republic of Panama, P. vivax malaria occurs less frequently than P. falciparum malaria. The ratio of malaria due to P. falciparum, P. vivax, P. malariae and mixed infections is 62:42:1:1.

P. vivax malaria is observed throughout the year, although the number of cases varies from month to month and from year to year. The largest number of cases is observed during the periods when change of season occurs.

A definite relationship exists between the incidence of malaria and the degree of development of sanitation. Although 28.4 per cent of the patients with P. vivax malaria seem to acquire their infections in sanitated areas, this figure is misleading. Most patients are unable to recall exactly where they have been over a period of time corresponding to the incubation period of malaria. As a general rule, their activities are not confined to sanitated areas. The incidence of malaria has been so effectively reduced by sanitation that the statement that a particular infection has been acquired in a sanitated area must be regarded with suspicion.

Infection with P. vivax may occur any time after birth. At least one fifth of the children with P. vivax malaria in Panama have had at least one attack of malaria by the end of their second year of life.

The fact that the malarial infections are frequently associated with other conditions, particularly intestinal helminthiasis, must be fully appreciated in treatment of children living in the tropics.

The malignant cerebral and algid forms rarely occur in P. vivax malaria, although they are observed in malaria due to mixed infections.

Abnormal physical signs are uncommon in primary P. vivax malaria. Splenomegaly, hepatomegaly, pallor and subnormal weight are frequently observed in recurrent malaria. Because of the frequency of associated unrelated infections, it is difficult to determine conclusively which infection is predominantly the cause of existing symptoms and abnormal physical signs.

The differential diagnosis of malarial parasites in thick and thin blood smears depends on the recognition of features characteristic of infection with each species of parasite.

Periods of renewed activity are more common in P. vivax than they are in P. falciparum malaria. The absence of demonstrable parasites in the peripheral blood does not mean that infection has been cured. Usually patients return to their homes in unsanitated areas, where they may either have periods of renewed activity or become reinfected. Although available evidence favors the former, the final differentiation between relapse and reinfection cannot be made.

The latent malaria prevalent in children who live in unsanitated areas is not malaria without serious clinical manifestations. During periods of renewed activity it resembles the malaria observed in children in hospitals.

Complications, sequelae and deaths from P. vivax malaria are uncommon.

Quinine offers no material advantages over quinacrine hydrochloride so far as toxicity, effect on fever and number of paroxysms after institution of therapy are concerned. Both are equally effective in the treatment of the early acute attack of malaria. Quinacrine hydrochloride destroys the gametocytes of P. vivax and P. malariae, but is ineffective against the gametocytes of P. falciparum. Quinine probably does not directly destroy gametocytes but destroys the schizonts from which gametocytes develop. The determining factor in the efficiency of action seems to depend on the plasma concentration of each of these drugs.

Quinacrine hydrochloride is a highly effective drug in the treatment of all forms of malaria in children.

News and Comment

Certified in the Subspecialty of Allergy.—On Oct. 1, 1946, the following physicians were certified in the subspecialty of allergy by the American Board of Pediatrics in cooperation with the Committee on Allergy of the American Board of Internal Medicine. All were certified on the record without examination.

Certificate No.	Name
1.	Dr. Oscar M. Schloss, 125 East Seventy-Second Street, New York
2.	Dr. Lewis Webb Hill, 319 Longwood Avenue, Boston
3.	Dr. William Potter Buffum, 122 Waterman Street, Providence, R. I.
4.	Dr. Bret Ratner, 50 East Seventy-Eighth Street, New York
5.	Dr. Jerome Glaser, 300 South Goodman Street, Rochester 7, N. Y.
6.	Dr. Joseph Harman Fries, 25 Plaza Street, Brooklyn 17
7.	Dr. John E. Gundy, 264 King Street, Port Chester, N. Y.
8.	Dr. Arthur J. Horesh, 10515 Carnegie Avenue, Cleveland
9.	Dr. Samuel J. Levin, 469 Fisher Building, Detroit 2
10.	Dr. W. Ambrose McGee, 1601 Monument Avenue, Richmond 20, Va.
11.	Dr. Benjamin Zohn, 1449 Union Street, Brooklyn 13
12.	Dr. Orlindo L. Ross, 9 Exchange Place, Salt Lake City

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

RESISTANCE OF THE STRAIN OF PNEUMOCOCCUS TO SULFATHIAZOL, SULFAMETHYLTHIAZOL AND SULFAMETHYLPYRIMIDINE. L. BYLMER and J. MULDER, Nederl. tijdschr. v. geneesk. **86**:2626 (Oct. 24) 1942.

The American type I strain of pneumococcus, resistant to sulfapyridine, proved equally resistant to sulfathiazole, sulfamethylthiazole and sulfamethyldiazine.

van Creveld, Amsterdam, Netherlands.

A METHOD FOR THE DETERMINATION OF THIAMINE PYROPHOSPHATE IN THE BLOOD. H. G. K. WESTENBRINK, E. P. STEYN PARVÉ, A. C. VAN DER LINDEN and W. A. VAN DEN BROEK, Nederl. tijdschr. v. geneesk. **87**:1212 (July 10-17) 1943.

A modification of the manometric method for the determination of thiamine pyrophosphate is described. With this method extremely small quantities of this substance, dissolved in any quantity of fluid, can be determined. With blood, an accuracy of 1.0 microgram per hundred cubic centimeters is attained. Only 2 cc. of blood is required for a determination. The thiamine pyrophosphate content of the blood of normal human subjects and of oxen, newborn calves, sheep, pigs, a horse and albino rats was determined by this method. The average value for twenty samples of human blood was found to be 11.2, or 1.5 micrograms per hundred cubic centimeters.

VAN CREVELD, Amsterdam, Netherlands.

Metabolism; Infant Feeding; Milk and Other Foods

A COMPARISON OF THE NUTRITIVE VALUES OF DEXTROSE AND OF CORN SYRUPS AND OF THE EFFECTS PRODUCED ON THEIR UTILIZATION BY THIAMINE. CURT P. RICHTER, Am. J. Physiol. **145**:107 (Nov.) 1945.

The author has carried out experiments in order to obtain information concerning the nutritive value of syrups and the part played in their utilization by thiamine. It was found that 11 female rats of a standard age and weight survived forty days on the average on a diet in which a corn syrup (Special Corn Syrup) constituted the sole source of nourishment; 8 rats on another corn syrup (Sweetose) survived forty-one days on the average, and 21 rats on dextrose survived thirty-seven days on the average. When given access to a 0.02 per cent solution of thiamine the rats of all three groups lived almost twice as long as on the single food alone, seventy-six days on Special Corn Syrup, seventy-eight days on Sweetose and seventy-four days on dextrose. Both without and with access to thiamine the rats on the two syrups drank more water than did the rats on dextrose, because they were forced to take water with their syrup in the mixture, while the rats on the dry dextrose could take their water separately. The conclusion is reached that the two corn syrups have essentially the same nutritive value as dextrose and that thiamine has the same effect on their utilization.

STOESSER, Minneapolis.

THE PLASMA PROTEIN CONCENTRATIONS AND ORGAN WEIGHTS OF RATS ON A HIGH PROTEIN DIET. JAMES H. LEATHEM, Endocrinology **37**:157 (Sept.) 1945.

It has been shown that an important relation exists between the adrenal cortex and the concentrations of serum protein. Administration of adrenal cortex extract

to hypophysectomized rats will largly prevent the fall in serum albumin usually evident after removal of this gland, but it does not prevent the rise in globulin concentration. In this study the author sought to determine whether a high protein diet would influence the albumin-globulin concentrations of the normal rat, possibly by increasing the adrenal cortical function. The albumin-globulin concentrations of hypophysectomized rats fed either a high protein diet or the stock diet ad libitum were further subjects for study in this investigation.

It was found that concentrations of albumin and globulin in the plasma were not significantly altered in normal or hypophysectomized rats fed a diet high in protein ad libitum in comparison with rats on a stock diet. A voluntary reduction in food consumption resulted with a diet high in protein. This reduction was sufficient to reduce total protein levels in pairs of rats fed on stock diet, due to a decrease in albumin concentration in the plasma. Decided changes in albumin-globulin concentrations were evident following hypophysectomy, irrespective of diet. A diet consisting of 78 per cent of casein did not cause adrenal hypertrophy, nor was the weight of the pituitary, thyroid, testes, seminal vesicles, ventral prostate or spleen altered. This diet high in protein, caused a definite renal hypertrophy in normal rats but was without effect in hypophysectomized rats.

JACOBSEN, Buffalo.

Vitamins; Avitaminoses

CASE OF BERI-BERI IN AN INFANT. ANNIE SCHONDEL, Nord. med. (Hospitalstid.) **15**:2397 (Aug. 29) 1942.

An infant boy aged 6 months who had suffered from chronic dyspepsia with gray feces and malnutrition for five months displayed increasing edema. The thiamine content of the blood and the urine was subnormal. He was treated with injections of thiamine hydrochloride. A fortnight later the edema had disappeared and at the same time he had lost 750 Gm. of his body weight. The dyspepsia continued until he was 1 year old. Then he rapidly gained in weight, the condition became satisfactory and the excretion of thiamine was normal.

WALLGREN, Stockholm, Sweden.

SEASONAL VARIATIONS OF THE VITAMIN C CONTENT OF THE BLOOD. URBAN HJÄRNE, Svenska läk.-tidning. **39**:221 (Jan. 23) 1942.

Analyses are reported of the vitamin C content of the blood from December 1939 to December 1940 in 152 children aged 7 to 14 years. In December 1939 the blood contained 0.38 to 0.54 mg. per hundred cubic centimeters; in April 1940 it contained 0.17 to 0.26 mg. per hundred cubic centimeters, and in October 1940 it contained 0.67 to 0.79 mg. per hundred cubic centimeters. There were no significant differences due to the age, the sex, the economic level and hygienic standards of the home or the general state of health of the children.

WALLGREN, Stockholm, Sweden.

RICKETS IN BREAST-FED INFANTS. J. CLAUSEN, Ugesk. f. læger **104**:38 (Jan. 8) 1942.

Clausen reports on 4 cases of rickets in infants aged 5 to 7 months who had received breast milk. The mothers were healthy and had received an adequate diet during lactation; in addition they had been given 300 to 1,200 international units of vitamin D daily during the last six weeks to six months. The infants had not received an extra supply of vitamin D. The author stresses the importance of giving vitamin D to breast-fed babies and points out that the amount of vitamin D which the mother excretes in her milk often is insufficient for the infant although the mother receives extra vitamin D.

WALLGREN, Stockholm, Sweden.

THE QUANTITY OF NICOTINIC ACID IN URINE. J. A. NIEMEYER, Nederl. tijdschr. v. geneesk. **86**:78 (Jan. 10) 1942.

Among the different methods found in literature for the determination of the quantity of nicotinic acid in urine the author found that of Harris and Raymond the most useful and accurate. The daily excretion of nicotinic acid in the urine of 40 subjects, normal persons and patients of either sex, was determined. The opinion of Harris and Raymond that an excretion below 3 mg. a day would be pathologic could not be confirmed; even in a case of pellagra levis the excretion was above the average. The excretion by normal persons and by patients is extremely variable from day to day, and so it seems that from a clinical point of view the determination of the excretion of nicotinic acid is not of great value.

VAN CREVELD, Amsterdam, Netherlands.

SHOULD TREATMENT WITH VITAMIN D BE GIVEN ORALLY OR PARENTERALLY? J. VAN LOOKEREN CAMPAGNE and A. J. J. RODENBURG, Nederl. tijdschr. v. geneesk. **86**:419 (Feb. 21) 1942.

A report is made of the disappointing results obtained with intramuscular administration of vitamin D_2 as well as of D_3 in single doses of 7 mg. to infants, who subsequently showed good response to the oral administration of the same dose of the identical preparations.

VAN CREVELD, Amsterdam, Netherlands.

VASCULARIZATION OF THE CORNEA AND LACTOFLAVIN DEFICIENCY. E. C. GRAVEMEYER and R. LUYKEN, Nederl. tijdschr. v. geneesk. **86**:762 (March 28) 1942.

Vascularization and clouding of the cornea were seen in rats fed with various rations poor in lactoflavin. Among young animals the frequency varied. In adult animals, however, the manifestations were observed in 100 per cent of the cases. Adult animals were for this reason the best subjects for a study of these manifestations of lactoflavin deficiency.

VAN CREVELD, Amsterdam, Netherlands.

Hygiene; Growth and Nutrition; Public Health

CHILD HYGIENE AMONG THE AMERICAN INDIANS. SAMUEL X. RADBILL, Texas Rep. Biol. & Med. **3**:419, 1945.

For those interested in the folklore of medicine as well as in the historical phase of pediatrics this rather comprehensive review of various phases of child hygiene among American Indians of both the pre-Columbian era and more recent times will be found to contain valuable information. The following features are a few of those mentioned by the author.

Knowledge of the pre-Columbian Indian child is derived mainly from the study of skeletal remains. Deformation of the skull, which is apparent in the oldest archeologic findings, was artificially produced throughout large parts of North and South America chiefly for cosmetic effect. Other kinds of physical deformities are described, including hydrocephalus, symmetric osteoporosis, spinal deformities, clubfoot and harelip. Rickets is remarkable for its rarity.

Among the Indians of the post-Columbian era more information is available. Although parental love was certainly not lacking, infanticide was practiced everywhere for one reason or another. Weaklings, congenitally deformed infants, twins and children with other deviations from the norm were disposed of frequently. Many tribes did not hesitate to do away with infants that imposed hardship or inconvenience on the group. For religious purposes children were sacrificed, at times in great numbers.

The care of the newborn is described at some length. The initial bath and purification ceremonies entailed endless variations. Hardening processes were resorted to in order to eliminate weaklings. Several accounts are detailed describing the almost universal practice of swaddling and the various types of

Indian baby boards and cradles, with the inevitable hygienic, symbolic and superstitious appurtenances. Severing and treatment of the umbilical cord varied as it does with all races. Superstitious and religious rites accompanied the child's every care as much as it does in modern society. The ancient Mexicans had many deities specifically concerned with the individual phases of child welfare.

Breast feeding was the natural and universal form of infant feeding. It varied in manner and duration, but ordinarily lasted as long as the milk supply held out and the child desired to nurse. Wetnursing was widely used under the urge of necessity. Artificial feeding was usually haphazard, although many diverse feeding practices are recorded. To increase the flow of milk in the mother's breasts various galactagogues (of questionable virtue) were utilized. The Aztecs had a complicated formula, the Hopi gave decoctions of milkweed, the Delawares favored onions, the Cheyennes turned to various indigenous plants, the Cherokees used smooth sumac and the Pawnees gave infusions of skeleton weed. Curious instances of lactating old women and even of lactating men are mentioned.

Among the diseases of children discussed in more or less detail are tuberculosis, congenital syphilis, troubles with dentition, marasmus, epilepsy, paralysis, smallpox, measles and intestinal parasitism. Then follow descriptions of the treatment of sick children culled from various sources to indicate the variety of therapeutic practices to which the Indian healer resorted. An extensive materia medica was known to the aborigines on an empiric basis; indeed, many of the drugs used have found their way into the present day pharmacopeia. The article finally concludes with an extensive list of superstitious beliefs concerning the care of children.

The paper as a whole gives the facts as they were found pertaining to children as nearly as possible just as reported by the original observers. No attempt is made to evaluate the authenticity or to interpret critically the folkloristic ideas presented. The author merely intended to present certain source material as he found it without any comparative analyses to similar folk practices all over the world throughout the ages.

HANSEN, Galveston, Tex.

Prematurity and Congenital Deformities

POLYDACTYLY AND ANTERIOR HORN CELLS IN FOWL. LISBETH BAUMANN and WALTER LANDAUER, J. Comp. Neurol. **79**:153 (Aug.) 1943.

Baumann and Landauer made counts of the motor nerve cells in the lumbosacral region of 8 adult fowls which had five toes on one foot and four toes on the other. For comparison, they studied 2 fowls with five toes on each foot, and 3 fowls with the normal number, four, on each foot. In the fowl the motor cells of the lumbosacral region may be grouped in six columns, and of these the cells of the dorsolateral and retrodorsolateral columns furnish most of the innervation of the leg and foot. The cell counts in these columns showed always a greater number of motor cells on the side with the extra toe. The authors consider that the asymmetry in the numbers of motor neurons occurs in consequence of hereditary asymmetries in peripheral structures.

ADDISON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

"A CASE OF SYMPUS DIPUS." LOUIS RESNICK, J. Obst. & Gynaec. Brit. Emp. **52**:515 (Oct.) 1945.

Sympus dipus is a fetal abnormality characterized by almost complete union of the lower extremities and terminating in a double foot, the sole of which is turned to the front. Only 12 cases have been found in the literature. The author presents a sympus dipus which was delivered easily in breech presentation. He gives a classification for the varieties of fusion of the lower extremities and presents four theories of the causation. He also points out that this type of monster alone

has one vein and one artery in the umbilical cord. The only aid in the diagnosis of such fetal monstrosities before delivery is the location of the fibulas on the medial aspects of the tibias on roentgen examination.

CUMMINGS, Evanston, Ill.

ARACHNODACTYLY WITH OLIGOPHRENIA. J. J. TERPSTRA and F. WENSINCK, Nederl. tijdschr. v. geneesk. **86**:1530 (June 20) 1942.

A report is given of 2 cases of Marfan's syndrome (dystrophia mesodermalis congenita) in conjunction with oligophrenia.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

EPIDERMOLYSIS BULLOSA IN THE NEWBORN. ROBERT A. BLACK, EMMANUEL WILHELM, CHARLES S. GILBERT and CLEVELAND J. WHITE, J. A. M. A. **129**:734 (Nov. 10) 1945.

A case of epidermolysis bullosa in a newborn boy with extensive involvement of skin and mucous membranes is described. The course was downhill with death at the age of 74 days in spite of treatment with penicillin. Pulmonary atelectasis and patent foramen ovale were also found at postmortem examination. Two older siblings had died apparently of the same disease. The two other siblings and the parents had no cutaneous abnormality. The case is believed to be one of the type described by Herlitz as epidermolysis bullosa hereditaria letalis.

BAIRD, Wauwatosa, Wis.

THE CRYING OF NEWLY BORN BABIES: II. THE INDIVIDUAL PHASE. C. ANDERSON ALDRICH, CHIEH SUNG and CATHARINE KNOP, WITH THE TECHNICAL ASSISTANCE OF GERALDINE STEVENS and MARGARET BURCHELL, J. Pediat. **27**:89 (Aug.) 1945.

This is the report of a study made during April 1944 of the actual crying of 50 babies in a well regulated hospital nursery. Four observers took turns in recording the amount of crying in minutes and the estimated causes of crying.

The amount of crying for the baby who cried least was 386 minutes during eight days, or 48.2 minutes a day. The baby who cried most totaled 1,947 minutes during eight days, or 243 minutes a day. The average crying per infant amounted to 936 minutes during eight days, or 117 minutes a day.

A definite correlation between crying and nursing care was noted: the more care, the less crying.

The distribution of the total crying time of the 50 babies was bell shaped. A graph of the crying of the average baby per day for eight days resulted in a smooth curve, while that of any individual infant climbed and fell in an irregular manner.

Three different methods were used to evaluate the relation of crying to gain in weight and to feeding. The results were vague except for that of one method which showed 17.8 minutes less crying daily in favor of the good feeders.

An attempt was made to estimate the causes of crying. Obvious causes, such as hunger, vomiting, and soiled and wet diapers, together with unknown reasons, were tabulated in minutes and the number of spells.

The most clearcut result of this study of the causes of neonatal crying is the demonstration of the importance of unknown reasons. In total minutes of crying, this group of reasons closely approaches the amount for hunger, and in the number of spells of crying the figure which represents unknown reasons exceeds that which represents hunger.

AUTHORS' ABSTRACT.

TRANSMISSION OF STREPTOMYCIN FROM MATERNAL BLOOD TO THE FETAL CIRCULATION AND THE AMNIOTIC FLUID. JOHN H. E. WOLTZ and MARJORIE M. WILEY, Proc. Soc. Exper. Biol. & Med. **60**:106 (Oct.) 1945.

Streptomycin, the antibiotic obtained from the mold Actinomyces griseus, was injected intravenously (250,000 units in 5.0 cc. of isotonic solution of sodium chloride) into 14 normal pregnant women in labor. Samples of cord blood, maternal blood and amniotic fluid were assayed for streptomycin. Within nineteen minutes the substance was found in cord blood and amniotic fluid, and the concentration was found to be less than that of maternal blood. The concentrations were extremely low in all three of the samples when three hours or more had elapsed since injection into the maternal circulation.

HANSEN, Galveston, Texas.

"THE INFLUENCE OF SOCIAL AND ECONOMIC FACTORS ON STILLBIRTHS AND NEONATAL DEATHS." DUGALD BAIRD, J. Obst. & Gynaec. Brit. Emp. **52**:217 (June) 1945.

The author has analyzed several thousand cases divided into three groups in order to compare stillbirths and neonatal mortality rates in different social classes. Infants of group 1 were delivered in a nursing home and belonged to social register group 1 and 2 under the care of a family physician. Infants of group 2 were hospitalized under the care of specialists and belonging to social groups 2, 4 and 5. Infants of group 3 were from private specialists' practice. In the three groups the stillbirth rates were 25.3, 20.4 and 10 respectively and neonatal mortality rates were 13, 34.5 and 8.1 respectively. The stillbirth rates of group 1, owing to the incidence of prematurity, were almost double those of the other groups. The patients in group 1 and 3 are in the same social class, and the difference in stillbirths and neonatal mortality are probably due to different standards of obstetric care. In group 2 the stillbirth rate is three times that in group 3, although the standard of obstetric care is the same. Over 30 per cent of the stillbirths in full term infants in group 2 are due to intrauterine death of the fetus from causes unexplained, to poor health and nutrition of the mother. Stillbirth and neonatal mortality rates will be most substantially improved by improvements in the standard of the health and nutrition of the mothers in group 2.

CUMMINGS, Evanston, Ill.

"THE INFLUENCE OF SOCIAL AND ECONOMIC FACTORS ON STILLBIRTHS AND NEONATAL DEATHS." DUGALD BAIRD, J. Obst. & Gynaec. Brit. Emp. **52**:339 (Aug.) 1945.

From the study of 8,800 patients the author concluded: A much higher incidence of prematurity is found in practice among the working class than among patients of the higher income bracket groups. There is also a higher incidence of extremely small infants. The causation of prematurity in the higher income group was largely obstetric, while in the other group more than half the causes are unexplained. The unexplained prematurity must be related to social and economic conditions. Surveys have shown that there is a striking difference in nutrition and physique in the women of the two classes. Since the war there has been a remarkable fall in stillbirth rates, especially in the group in which causes of prematurity were unknown. This is due to the improved social position of the lower income classes and to better diet and nutrition.

CUMMINGS, Evanston, Ill.

MORO'S REFLEX IN THE NEWBORN. F. STIRNIMANN, Ann. pædiat. **160**:1 (Jan.-Feb.) 1943.

Moro's clasping reflex has been observed in 250 newborn infants. The observations prove that it is not a simple reflex, but that there are variable reactions, among which one must distinguish the direction of abduction and adduction.

Ordinarily one of these directions prevails. As there is no real embracing, the reaction ought to be called reaction for shaking, but it cannot be labeled with fear. The results are compared with responses to jarring and quick motions.

AUTHOR'S ABSTRACT.

INCREASED OXYGEN INTAKE AND WEIGHT OF THE NEWBORN. F. DEMUTH, Ann. pædiat. **160**:203 (April) 1943.

Increased intake of oxygen causes a decrease of the birth weight in children and mice and retards growth in young mice.

AUTHOR'S ABSTRACT.

CEPHALOHEMATOMA FROM THE OBSTETRIC POINT OF VIEW. G. J. LUBBERS, Nederl. tijdschr. v. geneesk. **87**:1254 (July 24-31) 1943.

Lubbers surveys the recent literature on the cause, clinical course and diagnosis of cephalohematoma. A conservative treatment and administration of vitamin K are strongly recommended.

N CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

ALTERATIONS IN THE AUTARCEOLOGIC SUSCEPTIBILITY OF THE MOUSE TO EXPERIMENTAL POLIOMYELITIS BY ESTROGENIC SUBSTANCES. G. E. FOLEY and W. L. AYCOCK, Endocrinology **37**:245-250 (Oct.) 1945.

Certain selectivities in the occurrence of the paralytic form of poliomyelitis in a few of the many subjects exposed to the virus indicates that the circumstance determining the outcome of infection resides in the host rather than in the parasitic factor or the factor of exposure. The association of the paralytic disease with certain constitutional types suggests an endocrine dysfunction, and the suspected greater frequency with which the paralytic disease occurs during pregnancy, in view of the implication of the upper respiratory mucosa as the portal of entry of the virus, suggests that the economy of the estrogenic substances may be concerned with susceptibility.

Accordingly mice were treated with estrogens before being inoculated with the virus of poliomyelitis. The results are similar to those obtained earlier in monkeys —treatment with estrogen enhances resistance against infection by intranasal but not by intracerebral administration of virus.

JACOBSEN, Buffalo.

CONGENITAL ANOMALIES FOLLOWING MATERNAL RUBELLA IN EARLY WEEKS OF PREGNANCY WITH SPECIAL EMPHASIS ON CONGENITAL CATARACT. C. H. ALBAUGH, J. A. M. A. **129**:719 (Nov. 10) 1945.

A review of cases of congenital anomalies following maternal rubella early in pregnancy, as described in the Australian and American literature, is given. Nine additional cases are presented. In 7 of these cases the mother had rubella at some time between the second and the tenth week of pregnancy. In 1 case the mother had measles (morbilli) and in another the mother was exposed to measles (morbilli). Eight of the babies had congenital cataracts bilaterally, and the remaining baby had strabismus. Eight babies had congenital heart lesions. All were retarded in development.

BAIRD, Wauwatosa, Wis.

THE SPINAL FLUID IN HEINE-MEDIN DISEASE (ACUTE ANTERIOR POLIOMYELITIS). A. M. MARQUE, J. M. MACONE and C. R. GIÚDICE, Rev. neurol. de Buenos Aires **9**:248 (July-Sept.) 1944.

The authors report on the analysis of 129 specimens of spinal fluid taken in cases of anterior poliomyelitis during the epidemics of 1936 and 1942. The fluid was always clear, without xanthochromia, blood or spontaneous coagulation. The

Pandy reaction was positive in 37 per cent of the specimens; it was usually negative in cases in which the illness was of less than fifteen days' duration. Pleocytosis, characteristic of all cases, was most pronounced during the first few days and in the week following the appearance of paralysis. No relation was observed in the intensity of the disease, the types of paralysis and the number of cells in the fluid. The highest number of cells was 600 per cubic millimeter, on the sixth day, in a boy of 5 years with paraplegia; the lowest number of cells was 6.4 cells per cubic millimeter, on the eighth day, in a girl of 2½ years with paraplegia. The cells gradually diminished in number with the progress of the disease. They were mainly lymphocytes, with polymorphonuclear leukocytes in some cases. The authors failed to observe the predominance of polymorphonuclear leukocytes during the first twenty-four to forty-eight hours, as reported by Peabody. An increase in protein content was observed in almost all cases, especially during defervescence and after paralysis set in; the amount varied from 50 to 200 mg. per hundred cubic centimeters. The sugar was usually increased, except in 1 case (34 mg. per hundred cubic centimeters). There were no significant changes in the chloride content, which varied from 640 to 819 mg. per hundred cubic centimeters. The colloidal gold curve was normal in 38 per cent of the cases; in 62 per cent the curves were atypical. The Guillain test was made in 32 cases, with precipitation in the second zone in most cases. The Wassermann reaction was negative in all cases.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

IMPORTANCE OF OPERATION ON THE TONSILS WITH RELATION TO POLIOMYELITIS. HANS ZELLWEGER, Ann. pædiat. **160**:169 (April) 1943.

The relation between operations on the tonsils and poliomyelitis is examined in the light of the American literature and of the epidemic of poliomyelitis in Zurich, Switzerland, in 1941.

1. There are 128 cases known in the literature in which poliomyelitis occurred within a short time (less than one month) after tonsillotomy or tonsillectomy.
2. (*a*) In these 128 cases there was a remarkably high (otherwise never observed) percentage of patients (68 per cent) with bulbar development. (*b*) American authors also found that with a longer interval between tonsillectomy and the commencement of poliomyelitis there was an increase in the incidence of the bulbar form. This relation was also seen in our smaller number of cases; the differences in our cases lie within the margin of error.
3. We agree with the American literature that a previous operation on the tonsils has no influence on the general morbidity of poliomyelitis.

AUTHOR'S ABSTRACT.

DIPHTHERIA AFTER IMMUNIZATION. W. A. TIMMERMAN, Nederl. tijdschr. v. geneesk. **86**:820 (April 4) 1942.

An attempt was made to trace cases of diphtheria in patients who had had a complete series of immunizing injections at least two months before they contracted diphtheria. The diphtheria occurring in 116 thus immunized children showed a benign course. None of these patients died; in extremely few the clinical course was severe and in the great majority slight or very slight. Nearly half of these children did not receive antidiphtheritic serum.

In 704 nonimmunized children the disease had a less favorable course; 3 per cent died and in only 20 per cent was it unnecessary to administer serum.

All three types of diphtheria bacilli proved capable of breaking through the immunity. There were no indications for the supposition that the gravis type was more apt to do so than the mitis type.

VAN CREVELD, Amsterdam, Netherlands.

SOME FIGURES ON DIPHTHERIA. W. VAN ZEBEN, Nederl. tijdschr. v. geneesk. **87**:1534 (Oct. 2-9) 1943.

The author tries to explain the epidemic of diphtheria in Holland in 1942. He demonstrates that in the years 1918 and 1930 the number of cases of diphtheria was exceedingly great in this country. The increase in numbers of cases thus occurs at an interval of twelve years, and therefore the epidemic of 1942 could, in the author's opinion, be expected. The fact that this time the epidemic was so extremely extensive should be explained by the significant decrease in incidence of diphtheria in the preceding years. When, therefore, in 1940 diphtheria began to spread, the number of persons susceptible to this disease was large because the opportunity to become immune by an inapparent infection had gradually decreased. It is in accordance with this concept that at present the number of older patients with diphtheria is much larger than during former epidemics. In relation to the enormous increase in the number of cases the mortality of diphtheria has not increased in this epidemic. The increase took place in the towns as well as in the country; the increase in the country was slightly smaller than that in the cities. The great increase in the total number of cases of diphtheria in Holland in the autumn of 1942 must be considered, in the author's opinion, as an extremely large normal seasonable elevation.

VAN CREVELD, Amsterdam, Netherlands.

ACUTE ANTERIOR POLIOMYELITIS AND PREGNANCY. A. P. VAN DER WEY and W. P. PLATE, Nederl. tijdschr. v. geneesk. **88**:426 (May 6-13) 1944.

During the epidemic of poliomyelitis in Amsterdam in the summer months of 1943 8 patients were observed who were pregnant. The mean age of these patients was 24 years; 5 were primiparas. In 5 women the duration of the pregnancy was less than five months, 2 were in the sixth month of pregnancy and 1 was at term. Two of the 8 women died. Disturbances in micturition were observed in 1 of the 8 patients, disturbances of respiration in 3. There was no question of a recovery or of distinct improvement after abortion (contra Hansen, 1943). In one of the patients abortion occurred six weeks after the beginning of the disease; in another patient cesarean section at term had to be done because the increasing dyspnea caused paresis of the intercostal muscles. With the patient under local anesthesia cervical cesarean section was performed. The child had a weight of 3,100 Gm., cried immediately and developed normally. The placenta was macroscopically and microscopically normal. Four other children born spontaneously were normal. The fetus of 1 patient who died in the fourth month of pregnancy showed no changes microscopically in the central nervous system.

VAN CREVELD, Amsterdam, Netherlands.

DIPHTHERIA AND THE BLOOD PICTURE. W. B. VAN DER VELDEN, Nederl. tijdschr. v. geneesk. **88**:444 (May 6-15) 1944.

Two cases are reported to stress the great significance of blood tests for the diagnosis of diphtheria. The first case concerned a boy of 14 years, who fell ill with a sore throat and fever. As a fairly large membrane was visible on both tonsils and a younger brother was already suffering from diphtheria, the house physician injected antidiphtheritic serum and repeated this injection on the following days. No effect on the membranes was observed, and the general condition grew worse. In the hospital the diagnosis of acute aleukemic myeloid leukemia was made after examination of the blood picture and of the biopsy specimen from the sternum. Three weeks after his entrance into the hospital the boy died.

The second case was that of a patient with agranulocytosis after the use of Veramon (barbital derivate).

Both observations once more demonstrate that decrease in the normal quantity of granulocytes may be combined with the picture of diphtheroid angina. The

presence of such a diphtheroid angina necessitates a bacteriologic investigation of the throat (staining with carbolfuchsin to exclude Plaut-Vincent angina) and the examination of a blood slide (to exclude diseases such as mononucleosis infectiosa).

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

THE INCIDENCE OF TOXOPLASMIC INFECTIONS IN THE ST. LOUIS AREA. WILLIAM P. CALLAHAN JR., Proc. Soc. Exper. Biol. & Med. **59**:68 (May) 1945.

Because of a number of fatalities (8 since 1940) in the St. Louis area from toxoplasmosis, study of the serum was made of 100 apparently normal persons from 18 to 28 years of age. Four different groups were tested: 26 unmarried girls 17 to 26 years old who lived outside of the state of Missouri, an equal number who had been residents of St. Louis since birth, 25 married women who had had one or more normal children and 23 men 20 to 28 years of age. Organisms (B. D. strain of toxoplasma originally obtained from the case of a person dying of the disease) were maintained by intracerebral inoculations of mice, and they were injected into rabbits in various dilutions and also together with serum from the human subjects. Neutralization tests revealed that 2.7 per cent of the persons in the St. Louis area showed the presence of a definite inhibitory factor on the necrotizing action of toxoplasma in the skin of rabbits, whereas no positive results were obtained from the unmarried nonresidents, the married women or any of the men studied.

HANSEN, Galveston, Tex.

ARTIFICIAL INDUCTION OF SUBCUTANEOUS NODULES IN RHEUMATIC FEVER. I. ARTHUR MIRSKY, Proc. Soc. Exper. Biol. & Med. **60**:143 (Oct.) 1945.

Series of patients (men 19 to 40 years of age) with and without rheumatic fever were given injections subcutaneously over the ulna of 1 cc. of a 1 per cent solution of crystalline trypsin magnesium sulfate compound in saline solution, 1/400 molar hydrochloric acid or water (in some instances a 5 per cent solution of crude trypsin was used). Within two to three hours edema developed which persisted forty-eight hours. In patients convalescing from acute rheumatic infection, subcutaneous nodules developed in 70.3 per cent (102 of 145 patients). In the region of the injection, in patients from whom a previous history of rheumatic fever was elicited, 77.3 per cent (17 of 22 patients) had the lesions. Only 2.5 per cent (1 of 40 men) of patients who had suffered streptococcic infections of the throat (beta hemolytic streptococci on culture) two to three months previously had the nodules, and 13.3 per cent (10 of 75 men) of control patients, with no history of rheumatic fever in themselves or family, and no recent streptococcic throat infection had the change in the subcutaneous tissue. A small group of patients with rheumatoid arthritis behaved in a manner like the patients in the rheumatic fever group. It is yet to be determined whether this phenomenon in rheumatic fever patients is of any diagnostic or prognostic significance.

HANSEN, Galveston, Tex.

RELATION OF PLASMA LEVEL OF ATABRINE TO MORPHOLOGY AND MOTILITY OF PLASMODIUM VIVAX. WILLIAM TRAGER, FRED B. BANG and NELSON G. HAIRSTON, Proc. Soc. Exper. Biol. & Med. **60**:257 (Nov.) 1945.

Seven patients with Plasmodium vivax malaria having 500 or more parasites (P. vivax) per 500 white blood cells were given intramuscular injections of 200 mg. of quinacrine dihydrochloride in water. The propotrtion of normal motile parasites with finely dispersed pigment decreased greatly with the height of concentration of quinacrine in the blood, and instead nonmotile parasites with clumped pigment mass appeared. After three hours, when the quinacrine level fell off, the motile organisms again appeared in the blood of 4 of the 7 patients studied. No change in appearance or motility of the parasites was observed within

three hours after the oral administration of quinine, although the concentrations of quinine were 6 to 10 mg. per liter of plasma. The authors conclude that repeated injections of quinacrine are needed when malaria is treated parenterally with this drug.

HANSEN, Galveston, Texas.

A CENTURY OF CHANGES IN THE MORTALITY AND INCIDENCE OF THE PRINCIPAL INFECTIONS OF CHILDHOOD. A. H. GALE, Arch. Dis. Childhood **20**:2 (March) 1945.

In his review of a hundred years of death registration the Registrar-General gave a table which showed that in the first year of civil registration, from July 1, 1837 to June 30, 1838, there were 156,817 deaths in England and Wales among children under 15 years of age. By applying the death rates in different age groups in 1937 to the estimated population by sex and age at the end of 1837, he then calculated the number of deaths which would have occurred if the rates of 1937 had prevailed in 1837. The figure was 38,719, slightly less than a quarter of the actual number of deaths registered. These figures are for deaths from all causes and include deaths from conditions peculiar to infancy and from violence, the deaths from which have not decreased to anything near the same extent as have those due to infections. The reduction in mortality from infection has therefore been even more remarkable than these figures suggest.

This survey is the history of death from infections through 100 years. With the beginning of the twentieth century an all-round reduction of death rates of children, particularly of infants, began. The mortality of bronchitis and pneumonia began to fall, and the decline of tuberculosis, diphtheria and whooping cough was accelerated.

KELLY, Milwaukee.

TREATMENT OF OXYURIASIS. J. DRUKKER, Nederl. tijdschr. v. geneesk. **86**:180 (Jan. 24) 1942.

After a review of the diagnosis and the more familiar forms of treatment of oxyuriasis, the treatment with gentian violet medicinal is described. This method consists in administration on eight successive days of gentian violet medicinal in a dose of 15 mg. multiplied by the age of the child in years; after a week's interval the same treatment is repeated.

VAN CREVELD, Amsterdam, Netherlands.

OCCURRENCE OF LAMBLIA IN CHILDREN. C. SMEENK, Nederl. tijdschr. v. Geneesk. **86**:426 (Feb. 21) 1942.

The author reports observations concerning 32 patients with lambliasis. This infection is frequent in children and can cause many symptoms or none. The author recommends search for the presence of the organisms in each case of diarrhea which does not respond to diet, in cases of vague abdominal complaints existing for a long time, in all cases of pain in the right upper part of the abdomen, in chronic appendicitis, in cases of fatty stools and in cases in which abdominal tuberculosis is suspected but in which no large nodules can be felt.

VAN CREVELD, Amsterdam, Netherlands.

FURTHER OBSERVATIONS ON RAT BITE FEVER IN HOLLAND: A LABORATORY INFECTION. W. P. A. SCHÜFFNER and H. BOHLANDER, Nederl. tijdschr. v. geneesk. **86**:1341 (May 30) 1942.

A laboratory infection with rat bite fever resulting from the bite of a field-mouse is described. The urine of the mouse contained innumerable Leptospira organisms. The illness ran with high fever, ending with a crisis and followed by a brief recurrence. Leptospira grippotyphosa could be demonstrated in the patient's blood on the first day of his illness, but was not observed in the blood

withdrawn during the last attack of fever (the fifth). In contrast to the known facts the Leptospira organisms appeared again in the urine two months later, where at present (after four months) they still can be demonstrated.

VAN CREVELD, Amsterdam, Netherlands.

SOME CASES OF ASCARIASIS WITH A LETHAL COURSE. M. C. VERLOOP, Nederl. tijdschr. v. geneesk. **87**:1319 (Aug. 7-14) 1943.

A case is described in which Ascaris parasites not only had caused an obstruction of Vater's papilla, but had penetrated into the intrahepatic bile ducts, causing hepatitis, cholangitis and abscesses of the liver. In a second case the parasites had caused (spastic?) ileus, giving rise to peritonitis, which was the cause of the patient's death. In a third case the parasites had caused an obstruction of the bile ducts and of Wirsung's canal, giving rise to severe changes in the liver and the pancreas.

VAN CREVELD, Amsterdam, Netherlands.

A METHOD FOR THE DETECTION OF INFECTION WITH OXYURIS VERMICULARIS. N. H. SWELLENGREBEL and W. A. P. SCHÜFFNER, Nederl. tijdschr. v. geneesk. **87**:1363 (Aug. 21-28) 1943.

In looking for eggs of Oxyuris vermicularis one should take the material from the perianal skin and not from within the anus. Instead of using the NIH swab of Hall (1937) the authors recommend another method with which they obtained better results. Before taking a sample from the anal region, the authors prepare the perianal region with a thick-walled glass tube, 10 cm. in length, with a bulb having a diameter of 1.75 cm., the distal part of which is ground glass. The moistened bulb is compressed against the anus and rotated for ten seconds. In this way the heaps of eggs are loosened, separated from one another and suspended in the water with which the bulb had been moistened. This suspension is placed on an object glass with 1 drop of water. The drop is dried in the air and the preparation is ready. In this way the eggs are not damaged. Examination is performed in cedar oil or in paraffin oil, without covering the glass and with weak magnification. Some results obtained with this method are reported.

Examination of dirt from finger nails gave a wrong picture of the degree of infestation with Oxyuris parasites. In all schools with many parasite carriers the investigation of this material for the presence of Oxyuris eggs gave a positive result.

VAN CREVELD, Amsterdam, Netherlands.

LOCALIZATION OF MALARIA IN TOWNS. H. KRAAN and N. H. SWELLENGREBEL, Nederl. tijdschr. v. geneesk. **87**:1783 (Dec. 11-18) 1943.

It is characteristic of malaria in towns that it occurs much more frequently in the outer parts of the town than in the center, as was observed by Christophers in 1911. This observation was also made in 1920 in the Netherlands, when a study was made by Korteweg on the spreading of the disease in the town of Alkmaar in 1942, when the authors made a study of the distribution of the cases of malaria in the same town. They did not find more cases reported at the periphery of the town than in the center. However, when the frequency of malaria was not judged from the number of patients suffering from malaria but from the houses in which there lived school children with a palpable spleen, a more typical localization of malaria was found to be present. This contradiction between the results of two methods of measuring the frequency of malaria often appeared to be of importance when it was necessary to investigate which houses had to be freed from mosquitoes in the autumn. The large number of children with a palpable spleen suggests the presence of carriers of the parasites who are not suffering from malaria but still are able to infect the mosquitoes.

VAN CREVELD, Amsterdam, Netherlands.

INVESTIGATION ON THE FREQUENCY OF ENTEROBIUS VERMICULARIS (OXYURIS) IN FOUR GROUPS OF CHILDREN IN AMSTERDAM. F. H. SMALT, Nederl. tijdschr. v. geneesk. **88**:240 (March 11-18) 1944.

According to Drukker (1942) 10 per cent of the children in Amsterdam were infected with Enterobius vermicularis, in contrast to the much higher figures found in American towns. Smalt repeated this investigation, using the method of Hall (1937) with some slight modifications. In all 300 school children were examined. About 97 per cent were found to be infected with Oxyuris. The cause of the great divergence between these figures and Drukker's can be explained by the circumstances, by the use of a modified method and by the way in which the method was carried out.

VAN CREVELD, Amsterdam, Netherlands.

OCCURRENCE OF SHIGELLA DYSENTERIAE OF THE NEW CASTLE TYPE AND CULTIVATION OF DYSENTERY BACTERIA FROM THE STOOL. C. D. WESTERMANN, Nederl. tijdschr. v. Geneesk. **88**:242 (March 11-18) 1944.

Shigella ambigua and Shigella dysenteriae of the New Castle type until a short time ago could not be found in the Netherlands. However, since August 1943 from 3 cases S. ambigua and from 108 cases organisms of the New Castle type have been cultured in the municipal laboratories of Amsterdam (in the same period S. Sonnei has been cultured from 134 cases and S. paradysenteriae from 53). In these particular cases the micro-organisms, cultured rather regularly from the stools of patients with dysentery, corresponded to strain 88 described by Boyd (1932, 1938). The clinical course showed no peculiarities.

As regards the isolation of the organism of the New Castle type from the stool, the value of the culture medium of Leifson (1935) again is stressed, especially for the Flexner group.

VAN CREVELD, Amsterdam, Netherlands.

CASES OF DYSENTERY CAUSED BY SHIGELLA DYSENTERIAE NEW CASTLE, OBSERVED IN THE NETHERLANDS. R. T. SCHOLTENS, Nederl. tijdschr. v. geneesk. **88**: 245 (March 11-18) 1944.

The dysentery bacteria occurring most frequently in the Netherlands are the Sonne type of Shigella dysenteriae and the Flexner types V, W and Z of Andrewes and Innmann. However, in September 1943 strains were isolated from patients suffering from a clinically benign dysentery which showed all properties of the New Castle type. There was close serologic correspondence with strains of S. dysenteriae New Castle, type 88, as described by Boyd (1932). The patients lived in widely separated parts of the Netherlands.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

TEN YEARS' EXPERIENCE WITH BCG (EXPERIMENTAL AND CLINICAL). SOL ROY ROSENTHAL, MARGERY BLAHD and ELEANOR I. LESLIE, J. Pediat. **26**:470 (May) 1945.

In a study of vaccination with BCG in which special emphasis was placed on having adequate controls and in which the multiple puncture technic was used to introduce the vaccine, the following results were obtained:

1. BCG vaccination has been found to be entirely innocuous both locally and generally in animals studied over a period of ten years and in infants studied over a period of seven years.

2. Among 1,204 vaccinated children for whom no source of contact with tuberculosis was known, there were 3 in whom tuberculosis developed and 1 death from the disease; whereas among 1,213 controls, there were 23 who had tuberculosis and 4 deaths from the disease.

3. Among 98 vaccinated newborn infants who were in contact with tuberculosis following vaccination, there was 1 in whom tuberculosis developed and no deaths, whereas among 63 controls there were 4 patients with tuberculosis and 3 deaths.

4. Considering the contact and noncontact groups as a whole, there were 27 persons with tuberculosis in the control group, compared with 4 in the vaccinated group; there were 7 deaths from tuberculosis in the control group and 1 in the vaccinated group.

5. There were 10 cases of tuberculosis in siblings not included in the aforementioned control groups and 1 death from tuberculosis in this group. From these results, it may be concluded that in the first seven years of life BCG vaccination is of definite value in the prevention of tuberculosis.

AUTHORS' ABSTRACT.

PULMONARY TUBERCULOSIS, CHILDHOOD TYPE, OF MULTIPLE FOCI, IN A BOY NINE YEARS OLD. BERLANGA, Bol. méd. d. Hosp. inf., México **1**:61 (March) 1944.

The patient was first seen five years prior to the report, at a dispensary, and his case was carefully studied. He was sent to the hospital because the roentgenogram showed multiple Ghon tubercles, and there was a suspicion that one of those lesions was undergoing caseation. After several weeks in the hospital, where careful tests were done and roentgenograms were taken, the suspicion was not confirmed, and the patient was discharged improved. He was found to have 10 Ghon tubercles.

MADERO, México, D. F., Mexico.

INTRACUTANEOUS TUBERCULIN THERAPY IN OCULAR TUBERCULOSIS. LAURA CANDIA, WERNER BUSTAMANTE and ADRIAN ARAYA, Rev. chilena de pediat. **17**:123 (Feb.) 1946.

Thirteen of 20 cases of ocular tuberculosis in children ranging in age from 20 months to 14 years responded satisfactorily to repeated intracutaneous injections of tuberculin.

Weekly injections of highly diluted old tuberculin were used, rarely producing any significant focal, local or general reaction.

Contraindications to such treatment include active pulmonary foci and intercurrent nontuberculous infections.

PLATOU, New Orleans.

TUBERCULOSIS OF THE PERIPHERAL LYMPH NODES. JOSE MAESTRE HERRERO and JUAN ENRIQUEZ ANSLMO, Rev. españ. de pediat. **1**:822 (Nov.-Dec.) 1945.

This article is a review of the literature on tuberculosis of the peripheral lymph nodes and a general discussion of the pathogenesis, pathologic anatomy, clinical picture, differential diagnosis and treatment of the disease. A table of differential diagnosis is included, giving in tabular form the points differentiating the disease from acute and subacute nontuberculous adenitis, syphilis of the lymph nodes, leprosy and various types of tumors and granulomas of the lymph nodes. No new material is included in this article.

MILLER, Newark, Ohio.

DIAGNOSIS OF TUBERCULOSIS ACTIVITY FROM UNEQUAL HYPERERGIC TUBERCULIN REACTIONS. MILUTIN URBANY, Ann. pædiat. **161**:135 (Sept.-Oct.) 1943.

Symmetric unequal reactions to tuberculin, i. e. the Pirquet reactions described by Mayerhofer, can be divided according to my investigations into: (*a*) proximal-hyperergic ones, especially when the Pirquet test was made in horizontal position of the forearm, and (*b*) distal-hyperergic reactions, when the tuberculin spots were in a vertical position on the forearm.

The proximal-hyperergic reactions are observed mostly when children are seen in bed at the hospital; the distal-hyperergic reactions can be observed in children in the outpatient department, who are not confined to bed.

Both kinds have the same significance, that of a hyperergy. The distal-hyperergic action is only the mechanical consequence of the predominance of the vertical position of the forearm. With change of this position of the forearm, circulation of fluid (that in the little veins and the lymph) in the skin is also modified.

Unequal hyperergic tuberculin reactions have an advantage over other reactions for the diagnosis of tuberculosis at an early age; they allow the physician to get an exact diagnosis sooner and in an uncomplicated way. AUTHOR'S ABSTRACT.

Diseases of Blood, Heart and Blood Vessels and Spleen

SICKLE CELL ANEMIA, "A GREAT MASQUERADER" EASILY RECOGNIZABLE WITH ROUTINE USE OF DIAGNOSTIC PARAMETER. TRAVIS WINSOR and GEORGE E. BURCH, J. A. M. A. **129**:793 (Nov. 17) 1945.

Routine examination of all Negro patients for sickle cell anemia through a medical service of the Charity Hospital, New Orleans, has been successfully done by one of the following methods.

1. The sedimentation rate (in a Wintrobe tube) of venous blood drawn after a tourniquet has been left in place at a pressure between systolic and diastolic for six minutes is compared with that of the same blood after oxygenation. A difference in the two rates of over 20 mm. an hour indicates sickle cell anemia (98 per cent accuracy).

2. The sedimentation rate of ordinary venous blood after oxygenation is compared with that of the same blood after exposure to pure carbon dioxide for fifteen minutes. A difference of over 27 mm. an hour indicates sickle cell anemia.

Significant increases in the hematocrit reading of the blood treated with carbon dioxide over that treated with air was also noted.

The value of this rapidly performed test in dealing with acute medical and surgical problems is obvious.

BAIRD, Wauwatosa, Wis.

A SIMPLE DEVICE FOR TIMING PRECORDIAL MURMURS. MARTIN M. MALINER, J. Pediat. **26**:570 (June) 1945.

The first and most important thing to ascertain regarding a murmur is its relation to the normal cardiac cycle, that is, whether it occurs during systole or during diastole. This apparently is simple, but one is forced to admit that the commonest of all the errors in the diagnosis of valvular disease of the heart is to mistake systole for diastole and thereby misinterpret the significance of a murmur heard during those periods. The majority of physicians tend to trust their ability to appreciate cardiac rhythm to tell them which is the first sound and which is the second sound. This method is even unreliable to the experienced cardiologist; using the radial pulse as a guide is equally untrustworthy.

Appreciating the necessity for some simple measure for the proper timing of murmurs, the author made use of a chain slightly suspended about the neck approximately 1 inch (2.5 cm.) above the suprasternal notch with the chain slightly elevated in order to add tension to the muscles of the neck and so accentuate the concavity of the suprasternal notch. With this chain in position, the portion over the notch was either raised or lowered according to the cardiac cycle. During systole, the pulsations of the large vessels caused the neck to expand, elevating the chain, and during diastole the collapse of these vessels was associated with the dropping of the chain. These vessels are so proximal to the heart as to make the pulsations practically synchronous with the cardiac cycle, and the timing of the cardiac murmurs is accurate. AUTHOR'S ABSTRACT.

POLYARTHRITIS IN SICKLE CELL ANEMIA. H. G. BRUGSCH and DOROTHY GILL, New England J. Med. **231**:291 (Aug. 24) 1944.

Sickle cell anemia has long been known to simulate rheumatic fever. Huck was the first to describe cardiovascular involvement in patients with this form of anemia, and King and Janeway have emphasized electrocardiographic changes similar to those found in rheumatic fever, such as prolongation of the P-R interval.

Despite the fact that the high incidence of combined cardiovascular disease, pain in the joints and fever in sickle cell anemia is stressed in publications from the South (Wintrobe and Bauer), the frequent occurrence of these symptoms in Negroes living in the northern states has attracted scant attention.

A summary is given of 4 cases of sickle cell anemia found among 16 Negroes whose illness had been erroneously diagnosed as active or inactive rheumatic fever. These cases are from the New England Medical Center in Boston; 2 of the patients were children.

Four cases of sickle cell anemia are discussed in which the diagnosis was obscured by the presence of polyarthritis and of heart murmurs simulating rheumatic fever.

GENGENBACH, Denver.

RHEUMATIC ENDOCARDITIS IN VERY YOUNG SUBJECTS. R. POINSO and J. M. LAUGIER, Arch. franç. de pédiat. **2**:787, 1944-1945.

Although its occurrence is most exceptional, this disease may be found in the earliest years. It is confused frequently in the literature with acute articular rheumatism, of which it is practically always a sequel.

Numerous observations are cited from English and French clinicians to fortify the conviction that age is not necessarily a barrier. It is to be borne in mind, however, that acute endocarditis in the very young is usually concerned with a septic infection of serious import.

Of whatever origin the condition is, the evolution is apt to be insidious, under the mask of a fever, without localization and not necessarily accompanied with articular pains.

The onset varies in character. It may be signalized by:

1. Pleuropulmonary manifestations.
2. Fever of undetermined source.
3. Fever with an erythematous angina.
4. Swelling of one or more joints.
5. A meningeal syndrome.
6. Cardiac irregularities, possibly with fainting, dyspnea, cyanosis, edema, dilatation of the heart, hepatomegaly and a rapidly fatal course.
7. Irregular symptoms of a vague type, such as asthenia, emaciation, pallor, abdominal pain, diarrhea and transitory erythema.

The course of the invasion will then inevitably be characterized by the appearance of cardiac signs, the predominating one being mitral insufficiency; rarely one will find aortic insufficiency. In either case the murmur is always intense and often more or less musical.

Disturbances of rhythm, muffling of the bruit, dilatation and other evidences of myocarditis seem to be "almost obligatory," as the authors express it.

Signs of pericarditis, on the other hand, are not so constant, being observed in only about one third of the cases. Articular manifestations continue to be absent or extremely obscure; they are replaced by light, fugitive pains involving the larger muscles.

The evolution of rheumatic endocarditis in young children is variable, and complete return to normal is exceptional; in the great majority of cases the course is rapidly downward, and the younger the patient, the darker the prognosis.

Diagnosis rests on the development of a murmur in the course of an ill defined infection. Roentgenograms will show dilatation of the left side of the heart, and electrocardiograms will reveal a serious invasion of the myocardium.

Autopsy reveals Aschoff bodies and the usual phenomena of nonmicrobian myocardial insufficiency.

The acknowledged hopelessness of treatment is discussed.

AMESSE, Denver.

PERIARTERITIS NODOSA: EXPERIMENTAL STUDIES. ENRIQUE GALAN, Bol. Soc. cubana de pediat. **17**:333 (Sept.) 1945.

This is the second report by the author on the subject of periarteritis nodosa. It includes a report of the first case of the disease in Cuba in a child. Clinically, the picture was that of protracted fever of septic type, with polyarthritis, abdominal pain, endocarditis, leukocytosis, polynucleosis and eosinophilia. The child was observed over a period of three years, and during this time he suffered seven phases of activity of the disease. A diagnosis of rheumatic fever was made primarily. However, bizarre cutaneous eruptions developed, such as livedo reticularis, purpuric macules, papular infiltrations, necrotizing dermatomyositis of the abdominal wall and an acroasphyxic Raynaud-like syndrome of the tips of the fingers, nose and tongue, with a subsequent course toward gangrene and mutilations. It was noted that plasma fibrinogen was greatly increased during the active phases of the process. The child was improving when the report was published.

Experimental studies were carried out. Rabbits sensitized with horse serum according to the Rich-Gregory technic showed arterial lesions similar to those reported by these investigators and to the microscopic picture of periarteritis nodosa, but the clinical picture of this condition and the gross pathologic lesions of the arteries were not produced.

The author feels that the clinical and experimental observations were strongly suggestive of the allergic pathogenesis and the nonspecific causation of periarteritis nodosa and that sensitization of the arterial system may occur under the influence of any toxin, bacterial allergen or heterologous protein.

KEITH, Rochester, Minn.

HAND-SCHÜLLER-CHRISTIAN DISEASE WITH CUTANEOUS MANIFESTATIONS. W. BURCKHARDT, Dermatologica **86**:250 (Oct.-Nov.) 1942.

A 3 year old boy who had repeatedly suffered from otitis media showed at the age of 2½ years the triad of diabetes insipidus, protusio bulbi and typical defects of the skull. Pinhead-sized yellowish nodules covered with tiny scales, together with purpuric petechiae were seen, mostly on the chest. The scalp was covered with seborrheic-like scales.

The histologic picture showed subepidermal reticuloendothelioma without deposits of cholesterol.

Similar cases of reticuloendotheliosis with a more acute course were described under the name of Abt-Letterer-Siwe disease. Glanzmann and Walthard, who described such a case with similar cutaneous lesions, expressed the belief that this reticuloendotheliosis is an infectious disease sui generis and the deposits of cholesterol are secondary. In cases of the acute disease in children only a few inner organs show deposits of cholesteral (Abt-Letterer-Siwe disease). Only when remissions occur does Hand-Schüller-Christian disease with deposits of cholesterol develop. Cases with similar cutaneous manifestations were reported by Gottron, Attig and Höfer.

CURTH, New York. [ARCH. DERMAT. & SYPH.]

USE OF DRIED SERUM IN BLOOD GROUPING. T. HUIZINGA and L. J. ZIELSTRA, Nederl. tijdschr. v. geneesk. **86**:313 (Feb. 7) 1942.

The authors describe their use of dried serum, obtained by the method of Brinkman (1943), in the determination of blood groups. The dry serum proved to be

exceedingly useful; it was demonstrated that dry serum does not deteriorate in agglutinating titer on being kept in storage, as the liquid serums do.

VAN CREVELD, Amsterdam, Netherlands.

SURGICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS BOTALLI. S. VAN PRAAG, Nederl. tijdschr. v. geneesk. **86**:633 (March) 1942.

Praag reports a case of patent ductus arteriosus closed by surgical treatment, in a woman of 25 years. The operative steps and observations made are described.

VAN CREVELD, Amsterdam, Netherlands.

MONONUCLEOSIS INFECTIOSA WITH CEREBRAL COMPLICATIONS. G. H. W. JORDANS, Nederl. tijdschr. v. geneesk. **86**:689 (March 21) 1942.

A case of infectious mononucleosis with cerebral complications in a man of 20 years is described. The common signs and symptoms were not distinct; the cerebral symptoms dominated the picture.

VAN CREVELD, Amsterdam, Netherlands.

SICKLE CELL ANEMIA. H. C. VAN LEEUWEN, Nederl. tijdschr. v. geneesk. **86**:1802 (July 18) 1942.

The author describes a case of sickle cell anemia observed for three years in a 22 year old Negro. The clinical picture is given, including changes in the blood, the cranial bones, the long bones of the extremities and the vertebrae. Splenectomy had no objectively observable influence on the course of the disease. The illness terminated suddenly in death, which was probably caused by a thrombosis of the main branch of the right pulmonary artery, as was found at autopsy. A brief description of the changes found at autopsy is added.

VAN CREVELD, Amsterdam, Netherlands.

CHANGES IN THE HEART IN CASES OF CARBON MONOXIDE POISONING. P. M. J. SCHWEITZER and G. A. C. BOSCH, Nederl. tijdschr. v. geneesk. **86**:1810 (July 18) 1942.

After calling attention to the frequent occurrence of carbon monoxide poisoning, a description is given of the electrocardiographic changes found in this condition. Two forms can be distinguished, which are also often found in combination: One is transient and ascribed to temporary anoxemia of the heart muscle; the other occurs after a few days and is of longer duration, the cause probably being a severe anatomic lesion. The latter form is thought to be promoted by the previous existence of impaired coronary circulation; it is affected adversely by too early exertion. From this it is clear that early and thorough elimination of carbon monoxide from the blood is of great importance, as is continued and regular supervision of patients who have sustained the poisoning. Use should be made of electrocardiograms. The patients should have absolute rest as long as the abnormalities persist.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF ACQUIRED HEMOLYTIC ANEMIA WITH HEMOLYTIC AMBOCEPTOR. S. A. WESTRA, Nederl. tijdschr. v. geneesk. **86**:2053 (Aug. 15) 1942.

A case is reported of acquired hemolytic anemia in a young man of 18. The disease was characterized by the presence of a hemolytic amboceptor, active not only against the patient's own chromocytes, but also against those of the same blood group (A) and of group O (type of Dameshek). This case was complicated by an attack of thrombopenic purpura. Treatment consisted in splenectomy. Periarterial fibrosis was found.

VAN CREVELD, Amsterdam, Netherlands.

SPONDYLOLISTHESIS OF THE CERVICAL VERTEBRAL COLUMN WITH COMPRESSIO MEDULLAE IN THE KLIPPEL-FEIL SYNDROME. A. C. DE VET and J. M. J. TANS, Nederl. tijdschr. v. geneesk. **86**:2340 (Sept. 19) 1942.

The authors review the literature on cases of Klippel-Feil disease combined with neurologic symptoms. Only intramedullary processes or root compression have been found and only in 1 case has medullary compression been ascertained. The authors describe a case of Klippel-Feil disease with cervical spondylolisthesis combined with an unusually high degree of lordosis. When the patient was 56 years old symptoms of serious medullary compression developed. By surgical intervention a decompression of the medulla was effected; by implantation of a bony graft an attempt was made to prevent further development of the spondylolisthesis. The patient's condition improved greatly.

VAN CREVELD, Amsterdam, Netherlands.

CHANGES IN THE HEART IN CARBON MONOXIDE POISONING. J. R. BORST, Nederl. tijdschr. v. geneesk. **86**:2455 (Oct. 3) 1942.

The article of Schweitzer and Bosch on changes in the heart in cases of carbon monoxide poisoning (*Nederl. tijdschr. v. geneesk.* **86**:1810 [July 18] 1942) induced Borst to report on the electrocardiographic findings in a number of patients suffering from acute carbon monoxide poisoning.

VAN CREVELD, Amsterdam, Netherlands.

DURATION OF LIFE OF TRANSFUSED NORMAL ERYTHROCYTES IN A PATIENT WITH ELLIPTOCYTOSIS. W. J. H. BUNGENBERG DE JONG, Nederl. tijdschr. v. geneesk. **87**:1258 (July 24-31) 1943.

Owing to the variety of methods used there exists a difference of opinion on the length of survival of normal erythrocytes in their own surroundings. Moreover, the survival of transfused erythrocytes varies according to the methods used. One of these methods is the transfusion of blood, the red cells of which can be recognized microscopically. The author worked in the opposite direction (using the method adopted by Kirkegaard and Larsen in 1942) and transfused normal blood into a patient with elliptocytosis; in this way he found that the normal erythrocytes survived eleven days.

VAN CREVELD, Amsterdam, Netherlands.

DECREASE OF THE NUMBER OF NEUTROPHILE LEUKOCYTES AND LYMPHOCYTES IN TIMES OF WAR. A. J. L. TERWEN, Nederl. tijdschr. v. geneesk. **88**:200 (Feb. 26-March 4) 1944.

The author, a hematologist, had been struck by the fact that in determining the cell counts of the blood leukopenia was found more frequently than formerly. Therefore he compared 1,000 blood counts from the period May 27, 1942, to May 15, 1943, with the same number from the period July 2, 1938, to May 22, 1939. Cases of leukemia were excluded. It appeared that with a single exception there was always a distinct diminution, which for all kinds of white cells during the whole period amounted to 1,050 cells per cubic millimeter, i. e., 14 per cent of the mean quantity present at the point of issue. This decrease was for the most part (72.9 per cent) caused by a decrease of neutrophile leukocytes; 18.7 per cent of the decrease was caused by a decrease in the number of lymphocytes. The definite causes of these remarkable decreases are unknown. Probably they are related to the modified feeding.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat and Ear

DIGEST OF STUDY OF SPEECH CORRECTION IN CITIES OF 100,000 AND OVER. BERNICE RUTHERFORD, LILLIAN READ and MYFANWY CHAPMAN, Quart. J. Speech **32**:207 (April) 1946.

Forty-three cities with populations of one hundred thousand or more answered a questionnaire completely enough to give some information on the amount of

speech-corrective service available in these cities. The summary was as follows: 1. The lower the ratio of the school population to the number of speech clinicians the more adequate was the service rendered. 2. The itinerant teacher plan and semiweekly service were typical patterns and were not related to adequacy of service. 3. Service was inadequate generally. 4. The typical procedure to determine who needed speech-corrective service was a combination of clinical survey and observation of classroom, or some other referring combination. 5. Speech-corrective service was given to about 2 per cent of the elementary school population. 6. Speech clinicians in most cities were required to have either specialized training or a degree in speech pathology. 7. The questionnaire itself allowed some variation in interpretation.

PALMER, Wichita, Kan.

SYMPOSIUM ON OTITIS MEDIA IN INFANCY: PATHOGENESIS, BACTERIOLOGY, HISTORY OF ITS EVOLUTION, ANATOMY, PHYSIOLOGY AND ETIOLOGY. R. MACHADO, Arch. de med. inf. **11**:97 (July-Sept.) 1942.

The anatomy of the middle ear in the adult is compared with that in the infant. The physiology and physiopathology of the middle ear are discussed, and the commoner causes of otitis media in infancy are considered. Statistics concerning causative organisms are given.

BRIBIESCA, Zamora, Mexico.

SYMPOSIUM ON OTITIS MEDIA IN INFANCY: CLASSIFICATION OF OTITIS MEDIA. CLINICAL FORMS AND THEIR EVOLUTION, LOCAL AND GENERAL COMPLICATIONS. S. FUENTES CRUZ, Arch. de med. inf. **11**:106 (July-Sept.) 1942.

Otitis media in infancy is classified as acute, chronic and specific, with subclassifications. Acute otitis media is divided into simple, catarrhal, exudative and suppurative disease. Chronic into catarrhal suppurative and latent otitis media and otosclerosis, and specific into tuberculous, syphilitic and diphtheritic. The symptoms, evolution and complications of the various types are described.

BRIBIESCA, Zamora, Mexico.

SYMPOSIUM ON OTITIS MEDIA IN INFANCY; FORMS AND COMPLICATIONS; TREATMENT OF OTITIS; TREATMENT OF COMPLICATIONS; CONCLUSION. A. CODINACH, Arch. de med. inf. **11**:116 (July-Sept.) 1942.

Otitis media in infancy and complications in relation to its prophylactic, medical and surgical treatment are studied. A review is presented of cases in which treatments varied and in which there were special problems.

BRIBIESCA, Zamora, Mexico.

SWIMMER'S OTITIS: ETIOLOGY, SYMPTOMATOLOGY AND PATHOGENESIS. J. C. NIELSEN, Acta oto-laryng. **33**:31 (Jan.-Feb.) 1945.

Nielsen's view of the etiologic factors and the pathogenesis of bather's otitis is different from that which has hitherto been prevalent. He bases his theory on the examination of two series of cases, one during the summer of 1941 and one during the summer of 1943. In 1941 he examined bacteriologically 33 cases and came to the conclusion that about 90 per cent of the otitides were caused by pneumococci, that the infections were endogenous, arising from certain nasopharyngeal bacteria, and that impure bathing water played no etiologic role. As these conclusions were not in accord with the previously accepted view, he examined a further series of 20 cases during the summer of 1943.

Regarding the etiologic factors, Buchband in 1939 reported on 20 cases of mastoiditis. In 50 per cent the infecting organisms were hemolytic streptococci, in 28 per cent pneumococci and in 14 per cent anhemolytic streptococci. In these cases the involvement was particularly severe, with a mortality rate of 12.5 per cent. In 1939 Kettel reported on 23 cases of swimmer's otitis, in 92 per cent of

which he isolated either Bacillus coli or staphylococci or both from the ear and the nasopharynx. Mastoiditis occurred in 4 per cent.

Nielsen calls attention to Taylor's observations on the fall of body temperature in swimmers and to the fact that water forced through the nose into the nasopharynx washes away the protective layer of mucus over the cilia of the nasal mucosa and thus retards or completely abolishes ciliary activity. Damage to such a mucosa was demonstrated microscopically by David Mezz in 1940.

Nielsen's technic in his 1943 series was that of aspirating the tympanic secretion after myringotomy, thus avoiding the contaminating flora of the external auditory canal. In all 20 cases pure cultures of pneumococci were obtained. Of these, 65 per cent were type I, 15 per cent type II and 20 per cent type III. In his 1941 series types V, III, I and XXVII were noted. His patients were predominantly young males, which corresponds to the finding of Buchband. He seeks to explain this by the fact that the adipose layer of the female, being heavier than that of the male, protects her better against a fall of body temperature.

The symptoms observed were mild and ran an average course of ten days. Rhinopharyngitis was present in only 20 per cent of the cases. All of the patients had indulged in diving.

As bacteriologic examination of the water of Copenhagen swimming pools showed no pneumococci, Nielsen discards the thesis that impure water is an etiologic factor. He believes that the infection occurs by way of the eustachian tube and explains the fact that it was a pure pneumococcic infection and not a mixed infection by supposing that the pneumococci in the nasopharynx are especially susceptible to the effects of general and local reduction in body temperature.

GROVE, Milwaukee. [Arch. Otolaryng.]

Diseases of Lungs, Pleura and Mediastinum

TREATMENT OF ACUTE PNEUMONIA IN CHILDREN WITH ONE MASSIVE DOSE OF SULFATHIAZOLE. CARL FRIDERICHSEN and POUL SÖBYE, Nord. med. (Hospitalstid.) **15**:2397 (Aug. 29) 1942.

A report is made of treatment of 70 children with a single massive dose of sulfathiazole and of 59 children with repeated small doses of the same compound for four days. The therapeutic effect was the same in the two groups, but there were less toxic signs and the administration of the sulfathiazole was simplified by the treatment with the single massive dose.

WALLGREN, Stockholm, Sweden.

THE DIVISION OF THE LUNGS INTO SEGMENTS. W. J. POTHOVEN and E. HUIZINGA, Nederl. tijdschr. v. geneesk. **86**:237 (Jan. 31) 1942.

Following up previous investigations on this subject, the authors describe the division of the middle and the lower lobe of the right lung into segments corresponding with the anatomy of the bronchial tree. In the middle lobe this division is constant, the bronchus branching off ventrally and soon dividing into a medial and a lateral branch. In the lower lobe the relations are much more complicated, many anatomic variations occurring here. Exceedingly constant is the first dorsal bronchus as the first large side branch; next follows the cardiac bronchus, which is generally present; the next side branch, a ventral bronchus, is rarely absent as a separate branch. Finally, there is a bifurcation into a mediodorsal and a ventrolateral branch. Thus five segments can be assumed. In conclusion, a review is given of the segments of the right lung and of the way in which systematic bronchoscopy should be carried out.

VAN CREVELD, Amsterdam, Netherlands.

SEGMENTAL SPREADING OF DISEASES OF THE LUNG. E. HUIZINGA, Nederl. tijdschr. v. geneesk. **86**:481 (Feb. 28) 1942.

Determination of the pulmonary segments has importance for the pathology of the lung. Clinically it makes possible a more accurate localization, of which use

can be made in bronchoscopy and surgery—for instance, in atelectasis, pulmonary abscesses and bronchiectasis. The division into segments also has its theoretic importance: the extension of certain processes is made explicable with its aid. Postmortem specimens are described, and the distinct segmental distribution of tuberculosis, lobar pneumonia and carcinoma is demonstrated.

VAN CREVELD, Amsterdam, Netherlands.

BESNIER-BOECK DISEASE. C. ELSHOUT, Nederl. tijdschr. v. geneesk. **86**:1473 (June 13) 1942.

On the basis of observation of Besnier-Boeck disease in 90 patients, a review is given of its distribution with respect to age and sex and its frequency in successive years. A preponderance is found in the female sex and in the age class of 10 to 30 years, also in the age class of 30 to 50 years in women. A review is also given of the various localizations. In this connection the frequent occurrence of iritis and of an initial phase with erythema nodosum are striking. Many patients complain of general malaise and slight pulmonary symptoms; the disease, however, can also have a completely symptomless course in spite of severe pulmonary dissemination. Sixty-five per cent of all patients are healed within one-half to two years. Recurrence is rare. A familial occurrence was seen twice. The direct mortality is low. The Pirquet reaction was negative in 94.2 per cent of the cases.

VAN CREVELD, Amsterdam, Netherlands.

ISOLATED ROUND FOCUS IN THE LUNGS AS A SIGN OF THE "DISEASE" OF BESNIER-BOECK-SCHAUMANN. G. P. BAUER, Nederl. tijdschr. v. geneesk. **88**:235 (March 11-18) 1944.

Different changes of the lungs have been described in the disease of Besnier-Boeck-Schaumann. To these changes the author adds another, an isolated round focus in the lung which he found in 1 case of the disease and which must be regarded as an enlarged miliary focus.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PERSISTING LIVER DAMAGE FOLLOWING CATARRHAL JAUNDICE. GEORGE W. SALMON and ELLEN EHRENFEST RICHMOND, J. Pediat. **26**:533 (June) 1945.

Nine children and 7 adults were followed during an attack of acute catarrhal jaundice and into the convalescent period. The length of time of observation varied from forty to two hundred and twenty-five days. It was found that hepatic damage, demonstrable by the cephalin-cholesterol flocculation test and by the lowering of the diastasic activity of the serum, may persist for a period of a few weeks to several months after apparent clinical recovery.

AUTHORS' ABSTRACT.

LYMPHOSARCOMA OF THE BOWEL IN CHILDHOOD. GEORGE D. CUTLER, R. B. STARK and H. WILLIAM SCOTT JR. New England J. Med. **232**:665 (June 7) 1945.

In a recent ten year study of histologically verified malignant tumors at the Boston Children's Hospital, Farber found 75 (21 per cent) belonging to the leukemia-lymphoma group. Of these, 47 were classified as acute leukemia, 14 as Hodgkin's disease and 14 as lymphosarcoma. In the authors' 5 cases of lymphoma arising primarily in the bowel, 2 growths were of the lymphocytic variety, 2 were lymphoblastic and 1 was of the reticulum cell group. The youngest patient was 4 months of age and the oldest 7. All were boys. This is in keeping with the male predominance in occurrence reported in the literature. The youngest patient in this series, a 4 month old baby, had the classic symptoms of acute intussusception and at operation was found to have a tumor of the ileoiliac type, whose leading point was an intramural lymphosarcoma.

Two older patients had increasing constipation for four and three months, respectively, leading to fecal impaction. In 1 of these patients acute intestinal obstruction developed a few days after hospitalization and by means of a barium enema an ileocolic intussusception associated with a large tumor of the terminal ileum was revealed. The other patient proved to have a chronic colocolic intussusception resulting from lymphosarcoma of the cecum and the ascending colon. The presenting complaint in another patient was an essentially asymptomatic irregular abdominal mass filling the right lower quadrant of the abdomen. In the last patient bloody stools attracted attention to a lemon-sized intramural reticulum cell sarcoma of the rectum. This last patient recovered after the operation, remained well and showed no recurrences for fifteen months. The other 4 patients died after operation. The peripheral blood showed no detectable abnormality in any of these 5 patients at the time of admission. Terminally, however, the blood picture of lymphoblastic leukemia developed in 2. All 5 cases are reported in detail.

GENGENBACH, Denver.

THE CAUSE OF EPIDEMIC DIARRHEA, NAUSEA AND VOMITING (VIRAL DYSENTERY?). HOBART A. REIMANN, HOWE PRICE ALISON and JOHN H. HODGES, Proc. Soc. Exper. Biol. & Med. **59**:8 (May) 1945.

Broth garglings and suspensions of diarrheal stools, obtained from patients who were suffering from epidemic nausea, vomiting and diarrhea, after filtration were nebulized and applied to volunteer medical students. The heads of these students were placed in pasteboard boxes for five minutes at a time, exposed to the nebulized filtrates of the garglings which had been collected two to four hours previously. Of 32 volunteers, in one to twenty-one days (mostly one to four days) 17 had attacks of nausea, vomiting, diarrhea, malaise, headache and abdominal discomfort, most of which were mild. In 7 mild nasopharyngitis occurred in addition.

In 11 of the 21 volunteers who inhaled stool filtrates, similar symptoms developed in a similar period. No symptoms developed in 6 who inhaled nebulized serum. In 15 volunteers who swallowed capsules of the filtrates no significant symptoms developed. As a control the remaining 240 students were found to have 22 attacks during the declining phase of the epidemic. Thus 9 per cent of the control subjects suffered attacks of this infectious gastroenteritis in contrast to 53 per cent of the combined group of volunteers. The authors' results suggest that the disease is filtrable, is air borne, enters through the respiratory tract and is present in the oropharynx and the stools but not in the blood.

HANSEN, Galveston, Texas.

TREATMENT OF SPRUE WITH SYNTHETIC L. CASEI FACTOR (FOLIC ACID, VITAMIN M). WILLIAM J. DARBY and EDGAR JONES, Proc. Soc. Exper. Biol. & Med. **60**:259 (Nov.) 1945.

Striking clinical and hematologic improvement occurred in 2 patients with nontropical sprue after the daily intramuscular injection of 15 mg. of synthetic Lactobacillus casei factor as the sole therapeutic agent. The patients were a white man aged 51 years and a white woman aged 23 years for both of whom the diagnosis of nontropical sprue was justified on the basis of sore mouth, diarrhea, weakness, loss of weight (38 and 34 pounds [17.2 and 15.4 Kg.] respectively), pigmentation of skin, macrocytic anemia, leukopenia, impaired absorption of dextrose and vitamin A, excess fat in the stools and a characteristic gastrointestinal pattern on roentgen examination. The authors feel that it is reasonable to attribute the improvement to the specific effect of the folic acid (synthetic L. casei), although the possibility of spontaneous improvement could not be ruled out in these patients.

HANSEN, Galveston, Texas.

OBSERVATIONS ON A CASE OF DIFFUSE ADENOMATOUS POLYPOSIS OF THE LARGE INTESTINE TREATED BY TOTAL COLECTOMY. LEVEUF, LAURENCE and ROUECHE, Arch. franç. de pédiat. **2**:177, 1944-1945.

Special attention has been given during the past twelve years to the familial type of the condition reported on by the authors. The number of polyps and their dispersion throughout the canal are too variable to offer satisfactory criteria. It is recognized that certain forms are limited to the sigmoid and others to the descending colon while others represent total involvement of the large bowel, with or without inclusion of the rectum. Cases of terminal ileac polyposis embracing the entire small and large intestine have been described, as well as invasions of the gastric mucosa. Huguenin, Coffey and Augier have shown independently that it is not always possible to classify these growths through a study of their pathologic anatomy.

The clinical picture does not present features more constant; in cases apparently parallel, some will be accompanied with diarrhea and hemorrhage while others can be recognized only through roentgenography and systematic rectoscopy and show such mild subjective symptoms that a physician may not be consulted. The familial factor must always be borne in mind.

Daily lavage was carried out with a 10 per cent solution, and the patient responded so promptly that by October of 1942 he had gained 11 pounds (5 Kg.), and the stools were entirely normal. Within a month, however, the symptoms returned with increasing violence, and it was clear that radical measures were indicated. On May 29, 1943, complete extirpation of the colon was successfully accomplished. The subject made an excellent recovery and has resumed his usual vocation after several years of great suffering. Examination of the section removed at operation showed throughout the colon from the cecum to the sigmoid, numerous polyps of pinhead size, without ulceration. Histologic studies revealed typical adenomas either sessile or with a pedicle, with no sign of infection or ulceration.

While this disease is comparatively rare, it may be found at any time and should be kept in mind. The Mayo Clinic, for example, reported 19 cases in a bulletin published in 1936. It is extremely difficult to estimate the gravity, the duration or the termination of a given case. Death may often supervene if the least delay is observed between the onset of hemorrhage and the institution of radical measures.

AMESSE, Denver.

HEPATIC GLYCOGENESIS APPEARING IN THE COURSE OF AN ANGIOCHOLITIS. J. BOUCOMONT and P. CAZAL, Arch. franç. de pédiat. **2**:196, 1944-1945.

The case of an infant of 18 months is reported by the authors. Beginning on April 10, 1943, fever was observed, the temperature ranging from 37.5 C. (99.5 F.) to 39 C. (102.2 F.); feeding became very difficult, the baby was anemic, subicterus was noted and the urine was dark. On April 23, in addition to these symptoms, the liver was found to extend 4 cm. below the costal arch. The spleen was not enlarged. Malta fever, typhoid and infection of the urinary tract were eliminated.

On May 7, the thermic curve remained unchanged. The patient was much emaciated, but he did not have cachexia or any of the phenomena which might accompany a suppurative hepatitis.

The liver, however, now reached a level 8 cm. below the false ribs; it was smooth, hard and painless; there was no edema, purpura or ascites, but a collateral circulation was developing. Kala-azar was suspected on account of cough and bronchitis, but research in this direction was dismissed inasmuch as the spleen was not palpable. The cutaneous reaction for tuberculosis was negative. There was a trace of albumin in the urine, and urobilin was in slight excess; bile pigments were present but no acetone. The stools were free of ova and parasites. Reactions to Bordet-Wassermann tests were negative.

On May 8, hematologic examinations were inconclusive. The moderate anemia present seemed purely globular, and sternal puncture shed no light on the pathogenesis. The syndrome thus consisted of hepatomegaly, with febrile hepatitis and

a secondary anemia without splenic involvement. No satisfactory hypothesis could be reached. A puncture biopsy was indicated, and this maneuver revealed three pathologic changes which promptly led to diagnosis. There was an enormous increase of parenchymatous tissue; the portal spaces were filled with cells of inflammatory origin, and finally there was a sclerosis, especially periportal and to a lesser degree intertrabecular. The most plausible conclusion was that the condition was due to an overload of glycogen. Examinations of the blood showed that from a preliminary level of 0.95 Gm. per liter, the sugar content rose to 1.06 Gm. one hour and three quarters after an injection of 0.25 mg. of epinephrine.

Hepatic puncture on May 19 showed again that the hypertrophy was occasioned by an enormous accumulation of glycogen. A strong aversion to sugar developed in the infant at this time. The temperature continued to oscillate irregularly, occasionally reaching 39 C.; the appetite on the whole was better. Suddenly the picture changed. The hemogram became normal; the fever gradually subsided, and in twenty days recovery was complete.

There is a full discussion of the microscopic study of material obtained by puncture.

AMESSE, Denver.

DATA ON 212 CASES OF INFANTILE DIARRHEA. HÉCTOR SILVEIRA, Arq. de pediat. **15**:7 (Jan.) 1942.

According to statistics, in Porto Alegre (rural zone) during 1941, 231 children died during the first year of life for each 1,000 born alive; in Brazil, 150,000 children die each year from enteritis and diarrhea. In the 212 cases cited here, the patients were frequently between 11 and 15 months old; the incidence was the same for the two sexes; it was higher during the hot months (May and June). The body weight of the sick children was lower than normal in 94 per cent of the total cases.

The most frequent infectious agent was Salmonella. Rhinopharyngitis and, in 76 cases, dietetic disturbances were found. Four to six stools per day were passed in 50 per cent of the cases, and less than 3 or more than 6 in the other 50 per cent. Sulfathiazole and sulfaguanidine, 0.25 to 0.50 Gm. in twenty-four hours, were given as treatment (three to six days for sulfathiazole and five to six days for sulfaguanidine).

The best results were obtained with sulfaguanidine. Antidysenteric vaccines, lactic ferments and ascorbic acid had no decisive influence on the evolution of the disease. Relapses were more frequent when sulfathiazole was used. Complications had a higher incidence with sulfaguanidine. Two children died, one under treatment with sulfathiazole and the other under treatment with sulfaguanidine.

LOZOYA, México, D. F., Mexico.

PLASMOTHERAPY. C. F. THOMAS, Arq. de pediat. **15**:17, 1942.

The author reports that in many cases of dehydration in children isotonic solution of sodium chloride administered by vein is not useful because of its quick elimination. The patients have a good response to plasma. Plasma can also be used instead of whole blood in cases of hemoconcentration.

There is no danger of shock even when large quantities of plasma are given. Doses of 30 or 50 cc. per kilogram of body weight must be given on the first or on following days. A quick recovery and an increase of the weight curve have been observed.

Parenteral administration of fluids, diet and the routine therapy must also be used.

LOZOYA, México, D. F., Mexico.

"CACHECTIC PURPURA." GOMEZ, Bol. méd. d. Hosp. inf., México **1**:5 (March) 1944.

The author reports on 5 patients with similar complaints. All 5 began with digestive disturbances; they were severely malnourished and dehydrated and had

noticeable signs of polyavitaminosis. On admittance to the hospital, or shortly after, they exhibited purpuric spots distributed throughout the thorax and abdomen. The peculiar characteristic about this type of purpura is that the blood picture is normal: the platelets, the bleeding and the coagulation times are not altered.

After a discussion on the mechanism of production of this purpura, the author concludes that it is included both in the group of athrombopenic purpuras and in that of purpuras caused by vascular fragility.

The Hospital del Niño has adopted the designation cachectic purpura for all those purpuric pictures in which the platelet count is normal or slightly diminished, with normal bleeding and coagulation times in children who are severely malnourished from lack of nutritive elements or vitamin factors and who may or may not exhibit acute digestive disturbances.

MADERO, México, D. F., Mexico.

ACUTE INFECTIOUS ENTERITIS IN INFANTS. JOSE ENRIQUE CELORIA, Rev. Soc. de pediat. d. Litoral **10**:109 (May-Aug.) 1945.

This comprehensive and exhaustive treatise about acute infectious enteritis is not well suited for abstracting. A historical introduction presents a survey of the ideas of the classical French and German schools concerning the causation of diarrheas, especally the question as to whether alimentary damage or infectious agents are the main factors in diarrheas of the infant. The author stresses the increasing importance of diarrheas of bacillary origin as compared with other causes. The different suggestions for classification are discussed. The paper covers the enteritis caused by Shigella, Salmonella, typhoid and paratyphoid, the nonspecific infections (Bacteria coli, Enterococcus, Proteus, Bacillus pyocyaneus, Clostridium) and the diarrheas in parenteral infections. For each of these groups, a complete report of the bacteriology, biochemical and serologic reactions, epidemiology, pathologic anatomy, clinical symptoms, differential diagnosis and treatment is given.

SOLMITZ, Chicago.

ACUTE YELLOW ATROPHY OF THE LIVER IN CHILDHOOD. OTTO GEISER, Ann. pædiat. **159**:21 (Dec.) 1942.

The author's report on 4 cases of acute yellow atrophy of the liver in childhood, 3 of which occurred during a widespread epidemic of epidemic hepatitis. The fourth case was caused by mushroom poisoning. The symptoms and, above all, the chemical examination of the blood permitted the following conclusions:

1. Yellow atrophy of the liver cannot be considered as an illness *sui generis*, but must be regarded as a severe evolution of the epidemic hepatitis, the infectious genesis of which is proved.
2. In all 4 cases there was a fall in the blood sugar content, which had been seen in animal experiments, but so far had not been observed in human beings.
3. The protein content of the blood was decreased, and there were an inversion of the albumin-globulin ratio and an increase in the fibrinogen quotients. There were a deficiency of sodium chloride and of cholesterol in the blood, and severe hemorrhages with prolongation of the prothrombin time. A detailed discussion of these results is given.
4. The decrease of the alkaline reserves was noteworthy. This represents an organic acidosis, probably due in a high degree to the lactic acid present in the blood serum.
5. Severe icteric nephrosis was found in all 4 cases. The role of the bile in the genesis of the nephrosis is unexplained. At any rate, and contrary to the view of Eppinger, the bile content of the blood serum was definitely increased.

Nervous Diseases

FOLLOW-UP STUDY ON NINETY-THREE COLLEGE STUDENTS WITH EPILEPSY. LEONARD HIMLER and THEOPHILE RAEPHAEL, Am. J. Psychiat. **101**:760 (May) 1945.

This study represents a twelve year follow-up of 93 epileptic students at the University of Michigan. There was 1 epileptic for every 1,670 regularly enrolled students. Of the 93 studied, 67 were men and 26 women. Seventy of the group had grand mal attacks only; 5 subjects had petit mal only, and 15 had both. The age at the time of the initial attack ranged from birth to 33 years, with an average of 16.8 years.

Seventy-six per cent of the seizures were classified as idiopathic and 24 per cent as symptomatic in origin. There was fairly direct association of the attacks with increased fatigue, irregular habits, alcoholic overindulgence, academic stress and outside work. Twenty-nine per cent showed improvement while at college. In the follow-up group 52.7 per cent improved. For medical treatment diphenylhydantoin sodium seemed to be the drug of choice.

Sixty-seven per cent earned acceptable grades and 23.6 per cent unsatisfactory grades. Of the group 47.3 per cent graduated—3 in medicine and 6 in law; 8 obtained a Master's degree.

The authors concluded that the presence of seizures in persons with good intelligence need not constitute a barrier to academic training on the college level or to successful personal, social or vocational adjustment after leaving college.

JAHR, Omaha.

UNUSUAL CONGENITAL ANOMALIES OF THE LUMBO-SACRAL SPINE (SPINA BIFIDA). J. M. MEREDITH, J. Nerv. & Ment. Dis. **99**:115 (Feb.) 1944.

Meredith reports 3 unusual cases of spina bifida. The first was that of a 6 year old girl previously treated for an infection of the urinary tract who proved to have a complete spina bifida (occulta) throughout the entire lumbar portion of the spine and the sacrum. At operation large portions of the posterior bony canal below the twelfth thoracic and the first lumbar vertebra were observed to be absent, and the terminal roots of the cauda equina were gathered together in a cable of nerves, which extended along the sacrum posteriorly to a dimple in the skin just above the gluteal cleft. This was released, affording relief of tension on the cauda equina. The operation resulted in considerable improvement in the patient's sphincter control. This case illustrates the results of abnormal fixation of the cord or cauda equina in precluding the rostral migration which normally occurs with the lengthening of the spine.

The second case was that of a 22 year old man with weakness and atrophy of the left leg, saddle and genital anesthesia and definite bladder disability, in which roentgenograms revealed a pronounced congenital deformity of the sacrum. At operation the conus medullaris was found to be adherent to the inner dura at the level of the second bony segment of the sacrum on the left; it was surrounded by a large pad of fat. Partial freeing of the conus relieved tension on the cord and resulted in considerable postoperative improvement.

The third case was that of a 13 year old girl who had had a simple lumbosacral meningocele repaired at the age of 3 years, with excellent results and entire absence of symptoms until three months before the present admission, when severe pain in the legs and slight dysuria developed. There was a complete spinal fluid block, and myelographic examination with iodized poppyseed oil revealed a mass lesion at the level of the third lumbar vertebra, which after operative removal proved to be a large cholesteatoma. Postoperative recovery was complete. The author believes this combination of a large congenital tumor and a simple meningocele to be unique.

CHODOFF, Langley Field, Va. [ARCH. NEUROL. & PSYCHIAT.]

Psychology and Psychiatry

ELECTROENCEPHALOGRAPHY IN BEHAVIOR PROBLEM CHILDREN. CHARLES I. SOLOMON, WARREN T. BROWN and MAX DEUTSCHER, Am. J. Psychiat. **101**:51 (July) 1944.

Solomon, Brown and Deutscher studied the electroencephalograms of two groups of 20 boys each, one group comprising the best behaved and the other the worst behaved in a school class. The ages ranged from 13 to 16½ years. The author chose this age range to avoid correlations between age differences and the electroencephalogram, concluding that at the age of 13 years normal adult patterns are developed. Social, economic and cultural backgrounds were similar for the two groups. The authors found 12 abnormal electroencephalograms among the 20 best behaved children and 11 among the worst behaved children.

The authors then studied in an institution for delinquent boys the electroencephalograms of the 10 least and the 10 most delinquent boys, finding abnormal patterns for 4 of the former and 9 of the latter. There was no correlation of the electroencephalographic pattern and intelligence, efficiency of performance or personality.

The highest incidence of abnormal electroencephalograms was found in the most poorly behaved institutional group, and this the authors conclude may indicate a physiologic disturbance influencing behavior. In view of the high incidence of abnormality found in normal children and the presence of normal and abnormal electroencephalograms among children presenting the same type of behavior problems, the authors conclude that it is difficult to interpret the significance of the electroencephalogram in an individual case. The presence of abnormalities can be considered only as an additional, unfavorable personal factor.

FORSTER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

A RUNAWAY FROM HOME. HUGO STAUB, Psychoanalyt. Quart. **12**:1, 1943.

Although many elements participate in the production of a criminal, among which are economic and social factors, traditions, the level and form of civilization, politics, power and psychologic factors, Staub doubts whether there is a genuine criminal who is not one because of an inner conflict, i. e., anxiety feelings, feelings of guilt or a need for punishment. Reality often replaces the inner mechanisms of guilt and self punishment by pressing hard enough and by inflicting sufficient suffering to weaken the inner restrictions and relieve the inner anxiety, thus releasing the aggressive tensions. The author believes that in all criminals there is an emotional urge to act dissocially, which originates in an unconscious conflict. In prison a criminal may be calm and well adjusted, but when he is released he becomes shaky, disintegrated, unbalanced, inhibited and emotional except when committing a crime. The interplay between the reactions of society and the criminal's acting out of his unconscious fantasies of self punishment result in the development of a criminal character in the latter. In proof of his thesis, Staub offers the analysis of a 17 year old boy who showed compulsive tendency to run away.

The author emphasizes two points in discussing the case.

1. Running away is behavior which is in contradiction to the tendency of a child to cling to infantile dependencies. The child may run away because he is being treated badly in his home, or he may run away, as in the case cited, because he has feelings of guilt about his unconscious murderous and incestuous impulses. With the latter motive there are associated some pleasure gains—by running away the child can make his mother cry for him and want him back; he can take revenge on her, and he can imitate his father by appearing capable and self reliant.

2. In treating patients whose behavior is antisocial, it is necessary to modify the usual psychoanalytic procedure. Such patients are at first absolutely passive in treatment because they have strong feelings of frustration and disappointment to which they react by obstinacy. The analyst must be active in convincing the patient

of his willingness and ability to help and of his perception of the patient's inner problems. The patient will test the analyst by every means possible to see whether he means what he says. If the patient is a braggart, he must be shown that his exaggerated self confidence is an overreaction to his feeling of helplessness. He must be helped to lose his anxiety about his helplessness by his confidence that the analyst will stand behind him. With the adolescent, the analyst must appeal to his intelligence. The analyst's activity in this preparatory period is directed toward gaining the patient's confidence in order to establish a strong positive transference, to draw off the excess of anxiety and fortify the badly damaged self confidence and to permit the controlling and restraining forces of the ego to operate. This accomplished, the usual technic of psychoanalysis is employed.

PEARSON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

HEREDITY OF FAMILIAL JUVENILE AMAUROTIC IDIOCY. G. P. FRETS, Nederl. tijdschr. v. geneesk. **86**:1887 (July 25) 1942.

In connection with a recently reported case the heredity in a case of juvenile amaurotic idiocy formerly observed by the author is described. In this case 2 out of 3 siblings showed the disease. The pedigree is described in detail. In this family other cases of the condition could not be found, nor could cases of the infantile form. Several mental abnormalities, however, did occur, such as feeblemindedness, alcoholism, manic-depressive psychosis and abnormalities of character. Impaired vision also occurred. Moreover, in this case the patients were consanguineous. The significance of the greater incidence of consanguinity in rare hereditary diseases is discussed. Monohybrid inheritance with recessivity of the character is not assumed to exist in amaurotic idiocy, because this disease occurs exclusively, or nearly so, as a familial condition.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

EXSTROPHY OF THE BLADDER. ARTHUR A. SCHAEFER and SHIMPEI SAKAGUCHI, J. Pediat. **26**:492 (May) 1945.

Exstrophy of the bladder occurs about once in every 30,000 live births, and about 8 times in boys to once in girls. The cause of exstrophy of the bladder is not definitely known. The present accepted theory is that of arrested development. This arrest must occur before the tubular form of the embryo is completed. This is the only way that the multiple defects found associated with exstrophy of the bladder, such as hypospadias, umbilical hernia, inguinal hernias and separation or absence of the pubic bones, can be explained.

Operations for reconstruction of the bladder have been uniformly unsuccessful. Dr. Hugh Young is the only one to have successfully reconstructed a bladder with sphincter control in a case of this defect. This procedure is not recommended in the average case. At the present time transplantation of the ureters into the colon with subsequent removal of the bladder is the procedure of choice.

Three patients with exstrophy of the bladder are reported as having been operated on at an early age. Heretofore, patients with this defect had been operated on after several years of life. There had always been a great deal of difficulty both from maceration of the skin by the constant wetting and from kidney infections. When such patients are operated on early, these difficulties are overcome. The technical difficulties are not much greater than later in life. The right ureter is transplanted first. At the second operation the left is transplanted. The third operation consists of removal of the bladder and repair of the umbilical hernia. The ureteral transplants were all done by the Stiles-Mayo technic, as this seems to

be the simplest and most satisfactory technic in our hands. One patient was operated on at 9½ weeks, one at 10 weeks and a third at 2 years of age.

AUTHORS' ABSTRACT.

ACUTE PORPHYRINURIA IN CHILDHOOD. ERNST BAUER, Ann. pædiat. **161**:193 (Sept.-Oct.) 1943.

A case of porphyrinuria acuta in a child of 2½ years is described. Three more cases of the disease occurring at an early age, the only ones which the author could find, are reported briefly.

The discriminating facts in the anamnesis of these cases in comparison with cases of adults are pointed out.

The necessity of not overlooking the porphyrins, i. e. their colorless preliminary stages, at an examination of the urine before a laparotomy in a case with uncertain diagnosis with acute pains predominant is to be emphasized. The testing can be done in a most simple way.

AUTHOR'S ABSTRACT.

Diseases of the Ductless Glands; Endocrinology

THE EFFECTS OF PANCREATECTOMY ON GLYCOSURIA AND KETOSIS IN DOGS MADE DIABETIC BY ALLOXAN. ELIZABETH THOROGOOD and BERNARD ZIMMERMANN, Endocrinology **37**:191 (Sept.) 1945.

Although the glycosuria is more severe and the insulin requirement higher in alloxan-treated than in pancreatectomized dogs, the former are able to live much longer without insulin treatment and fail to have ketosis and diabetic coma. As a result of data from the experiments here reported, the hypothesis has been proposed that there is secreted by the pancreas a second endocrine factor which acts to increase the blood sugar but to prevent ketosis in the insulin-deficient animal.

JACOBSEN, Buffalo.

INFLUENCE OF ADRENAL CORTEX TREATMENT ON THE POTASSIUM AND SODIUM LEVEL OF THE BLOOD IN GRAVE CONDITIONS OF CHILDHOOD. LEOPOLDO CHIODIN, Rev. Soc. pediat. d. litoral **10**:57 (Jan.-April) 1945.

Insufficiency of the adrenal cortex invariably causes increase of potassium and decrease of sodium in the plasma. Ten children who suffered from different severe conditions (e. g., lymphosarcoma, severe burns, typhoid, leukemia and pneumonia) were chosen at random for treatment. The sodium and potassium levels were determined before and after treatment with adrenal cortex extract. In all cases, the potassium level was far above normal (17 to 20 mg. per hundred cubic centimeters), whereas the sodium level was either within normal limits or slightly below normal (320 to 340 mg. per hundred cubic centimeters).

No definite effect of the injection of adrenal cortex extract could be demonstrated. Those patients who recovered showed decrease of potassium and increase of sodium content, whereas in the fatal cases the increase of the potassium and the decrease of the sodium level went on and was not influenced by the adrenal cortex extract.

SOLMITZ, Chicago.

THE TWENTY-FOUR HOUR RHYTHM IN DIABETES. F. GERRITZEN, Nederl. tijdschr. v. geneesk. **86**:373 (Feb. 14) 1942.

After a description of the technic by which in the normal subject the twenty-four hour rhythm of diuresis can be followed, the question is considered to what extent the assumptions as to the constancy of the inner milieu need to be modified. The functions of the organs show a twenty-four hour rhythm; the composition of the blood is constant, whereas on the composition of the tissue fluid no definite judgment can as yet be given.

Next an experiment is described which is indicative for the condition present in diabetes and by which is demonstrated that the twenty-four hour rhythm in the blood sugar, diuresis and output of chloride and sugar can be so pronounced that it must be seriously taken into account in the treatment of diabetes.

It is pointed out in particular that by adoption of this new concept as a basis for insulin treatment, a considerable saving of insulin can be obtained.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF CARCINOMA OF THE ADRENAL CORTEX. P. J. VAN DER LEEUW, Nederl. tijdschr. v. geneesk. **86**:1143 (May 9) 1942.

A case of carcinoma of the adrenal cortex in a girl 12 years old is described. It is demonstrated that biopsy of the uterine mucosa, examination of the spinal fluid and determination of the serum potassium perhaps may be valuable aids to the differential diagnosis.

VAN CREVELD, Amsterdam, Netherlands.

ADMINISTRATION OF ORDINARY INSULIN COMBINED WITH PROTAMINE ZINC INSULIN IN ONE INJECTION. A. J. R. E. VAN SCHOONHOVEN VAN BEURDEN, Nederl. tijdschr. v. geneesk. **86**:1213 (May 16) 1942.

In treatment with rather large doses of protamine zinc insulin severe hypoglycemia may occur. In order to prevent this it is recommended that not more than 40 to 48 units of protamine zinc insulin be given in twenty-four hours. The hypoglycemia after breakfast and after dinner should be combated by adding old insulin to the protamine zinc insulin (Joslin). The technic of aspiration of old insulin and protamine zinc insulin into one syringe and of the subcutaneous injection of this combination of old and protamine zinc insulin is described. With a correct technic mixture of both insulins during aspiration and injection can absolutely be avoided, and the old insulin loses nothing of its immediate action on the blood sugar level.

The result of combined injections in suitable cases is illustrated with blood sugar charts.

VAN CREVELD, Amsterdam, Netherlands.

SUDDEN DEATH IN YOUNG PERSONS WITH ENLARGED THYMUS. J. P. L. HULST, Nederl. tijdschr. v. geneesk. **86**:1949 (Aug. 1) 1942.

Three cases are reported of sudden death in young persons with enlarged thymus glands. Once death ensued by pressure on the trachea, once as a result of violent emotion in a boy aged 11, in whom were found status thymicolymphaticus, hypoplasia of the adrenal glands, precocious closing of the sutures of the skull and chronic raised intracranial pressure with cerebral edema and capillary bronchitis. In the third case a girl, aged 15, during menstruation died while asleep as a result of pressure of the thymus, weighing 74 Gm., on the innominate vein.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ABSENCE OF THE PATELLAS. A. J. P. VAN DER BROEK, Nederl. tijdschr. v. geneesk. **86**:948 (April 18) 1942.

In connection with a case of absence of the patellas, a review is given of the occurrence of patellas in the fore and hind legs in the animal kingdom. The significance of the formation of a patella, as concerns the patella genus, is considered from a morphologic and functional point of view. At the same time it is shown that the patella is a sesamoid bone, the functional significance of which is to keep the quadriceps tendon at a certain distance from the axis of the joint. Flexor muscles the distal tendons of which, on contraction, increase the distance from the

joint axis and thereby increase their rotation never have sesamoid bones in their inserting tendons, except the short muscles of the thumb. The study of sesamoid bones from a functional point of view is briefly touched on.

VAN CREVELD, Amsterdam, Netherlands.

KASCHIN-BECK'S DISEASE. D. J. STEENHUIS, Nederl. tijdschr. v. geneesk. **86**:1137 (May 9) 1942.

A description is given of a girl of 12 years with a disease which has not yet occurred in Western Europe, but which is endemic in Southeast Siberia, in Korea and in Manchukuo. The epiphyses and metaphyses of the knuckle bones are especially affected, but in cases of serious disease the other bones are affected as well, which causes a general deformity. Of late iron intoxication is supposed to be the cause of the disease.

VAN CREVELD, Amsterdam, Netherlands.

CONGENITAL CLUBFOOT AND ITS TREATMENT. C. J. VAN DER BAS, Nederl. tijdschr. v. geneesk. **86**:1610 (June 27) 1942.

Congenital clubfoot is described. The opinions on the genesis of this malformation still differ; some of the theories are mentioned. It is emphasized that early treatment gives perfect results, operation then being unnecessary. Treatment of clubfoot is important not only from a functional but also from an anesthetic and a social viewpoint. In older patients operation must be recommended, especially since with the present technic the results are satisfactory.

VAN CREVELD, Amsterdam, Netherlands.

A RARE DISEASE OF THE SKELETON, WHICH MAY BE ACCOMPANIED BY PIGMENTATION AND BY ENDOCRINE DISTURBANCES OF FUNCTION. E. M. HESLINGA, Nederl. tijdschr. v. geneesk. **87**:1428 (Sept. 4-11) 1943.

A boy of 14 years showed the syndrome described by Albright and his co-workers in 1937. The symptoms, differential diagnosis and causation of the disease are discussed extensively.

VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

DISSEMINATED CONGENITAL OSTEOMAS OF THE SKIN WITH SUBSEQUENT DEVELOPMENT OF MYOSITIS OSSIFICANS: REPORT OF A CASE IN AN INFANT. FRANK VERO, GERALD F. MACHACEK and FREDERIC H. BARTLETT, J. A. M. A. **129**:728 (Nov. 10) 1945.

The case described is that of a boy in whom "bumps" on the left side of the scrotum, on the left leg and on other parts of the body were noted at birth. At 3½ months of age the child had lesions varying in size from 1 to 5 mm. in diameter, hard and gritty and freely movable over underlying tissue but firmly attached to the skin. Biopsy showed osteoma.

During the first year of life some of the lesions enlarged, some became smaller and in some there was spontaneous extrusion of a small concrement. Biopsy specimens taken at 11 months of age were reported as "heterotopic chondroosteomatous formation with necrosis." Roentgenographic studies revealed scattered shadows of calcium density placed just under the epidermis with no demonstrable changes in the bone. The diagnosis suggested was "calcinosis universalis."

At the age of 35 months surgical removal of a large mass deep in the left buttock was necessitated because the lesion interfered with the motion of the thigh. Sections made of this mass showed well differentiated bone with marrow and also masses of hyaline and fibrocartilage. Although the process did not seem typical, it seemed more closely to resemble myositis ossificans than anything else.

BAIRD, Wauwatosa, Wis.

"TRICHOMALACIE" (A HITHERTO UNKNOWN DISEASE OF THE SCALP). G. MIESCHER, Dermatologica **86**:227 (Oct.-Nov.) 1942.

In a 5 year old child, loss of hair was noticed eighteen months previously in two roundish areas, not sharply limited, near the vertex and on the occiput. These two spots improved with ultraviolet rays and local sulfur therapy, but a third spot developed.

The involved areas were at the time of this report about the size of a child's palm and irregular in outline. The center was almost without any hair, and at the periphery scanty hair or stumps, 1 to 2 mm. long, remained. Most of the stumps were gray or colorless, deformed and thicker than the rest of the hair. Growing from the same follicle were apparently normal hairs, which, however, were easily pulled out or broke off. The follicles themselves either looked normal or appeared as hyperkeratotic elevated points resembling lichen pilaris. The scalp in these areas showed a mild degree of scaling and few pustular lesions not around the follicles. The whole area was slightly tender to touch. The rest of the hair, the nails and the skin of the body were normal. Laboratory examinations did not offer any clues.

Histologic examination showed that after fixation with Bouin's fluid either the whole hair or only the peripheral part did not take up the normal trinitrophenol stain. The shaft is not a rigid structure but wholly amorphous, blown up, curved and fissured. Bacteria, but no fungi, were demonstrated inside the hair. Five months later, bacteria could not be demonstrated again, which is regarded as proof that they are only secondary invaders. The deformed hairs at that time showed dark brownish black pigmented lumps, which clinically gave the impression of black points in the follicles. The root of the hair showed disorganized matrix cells but no signs of inflammation.

The pathologic process consisted of disturbance of normal cornification and of formation of amorphous hair cylinders. It seemed to be of parasitic origin, but the causative agent had not been determined.

Therapeutically, roentgen rays, arsenicals internally and sulfur locally were beneficial. The disease, which was progressive in the beginning, had almost completely disappeared.

CURTH, New York. [ARCH. DERMAT. & SYPH.]

CONGENITAL ECTODERMAL DYSPLASIA OF THE ANHIDROTIC TYPE. O. KOALUND-JORGENSEN and J. F. CHRISTENSEN, Acta dermat.-venereol. **22**:1 (Feb.) 1941.

Congenital ectodermal dysplasia of the anhidrotic type is characterized by absence of sweat glands, deficient dentition, poor development of the scalp hair, saddle-shaped nose, atrophic rhinitis and occasionally absence of sebaceous and mammary glands.

A review of the literature produced 58 cases, to which the authors add 2 of their own. The patients of the 2 cases described were brothers, children of a consanguineous marriage.

Sections of normal skins were examined microscopically and showed the absence of sweat glands, sebaceous glands and hair follicles.

These patients suffered great discomfort due to the absence of sweat glands, with resulting lack of heat regulation. In hot weather or on exertion, the body temperature became elevated, and they suffered from headache and became dyspneic. Any febrile infection made them acutely ill.

In most of the authenticated cases in the literature the disease is familial. In all but 7 cases the patients were males, and it is suggested that, like hemophilia, the dysplasia is inherited as a sex-linked recessive.

ROBINSON, Washington, D. C. [ARCH. DERMAT. & SYPH.]

XANTHOMA TUBEROSUM WITH HEART FAILURE. A. H. SMEETS, Nederl. tijschr. v. geneesk. **86**:2120 (Aug. 22) 1942.

A case is reported of a girl 12 years old with xanthoma tuberosum, angina pectoris, cardiac damage resulting from the xanthomatosis and impaired hepatic

function. The raised cholesterol level was not affected by diet or administration of insulin, nor did any change in the condition of the xanthoma occur. After a complicating pulmonary tuberculosis was noticed no further attempts were made to treat the xanthoma.

VAN CREVELD, Amsterdam, Netherlands.

SODIUM CHLORIDE AS THE CAUSE OF STROPHULUS INFANTUM AND OF RELATED DISEASES IN CHILDHOOD. J. BOL, Nederl. tijdschr. v. geneesk. **87**:1261 (July 24-31) 1943.

The author concludes, from his own extensive experience, that about one ninth of all children in the Netherlands up to the age of 9 years suffer from strophulus infantum. He considers sodium chloride to be the cause of this condition and of the whole group of urticarial cutaneous diseases in childhood. In his opinion a better name for this group of diseases would be morbus salarius.

VAN CREVELD, Amsterdam, Netherlands.

A PECULIAR LIGHT DERMATOSIS, LOCALIZED ON THE EARS. M. RUITER, Nederl. tijdschr. v. geneesk. **87**:1327 (Aug. 7-14) 1943.

A father and his two sons had a peculiar disease, localized only on the helix and the anthelix, which showed numerous white elevations, resembling urticaria. There was no question of a real dermatitis. The condition appeared for the second time in the spring season, which pointed to a sensitivity to light. Histologically, besides a local elevation of the epidermis, only ordinary symptoms of inflammation could be found. In the literature this condition is described only by Jadassohn (1935) and by Burckhard (Zurich, 1942). Porphyrinuria was absent in the author's cases.

VAN CREVELD, Amsterdam, Netherlands.

CUTANEOUS TEMPERATURES OF PATIENTS SUFFERING FROM ERYTHROCYANOSIS CRURUM PUELLARUM AND THE INFLUENCE OF ESTROGENIC SUBSTANCES ON THESE TEMPERATURES. R. KOOIJ, Nederl. tijdschr. v. geneesk. **87**:1359 (Aug. 21-28) 1943.

The cutaneous temperatures of a number of patients with erythrocyanosis crurum puellarum were measured and, as was expected, were found to be lower than the cutaneous temperatures of normal girls. The patients generally had a thick-set figure, characterized especially by accumulation of fat on the nates, mammae and hips (*typus rusticanus*). They also often complained of disturbances of menstruation. The influence of the administration of estrone on the cutaneous temperature was studied. It appeared that injections of estrone preparations had a transitory effect on the cutaneous temperature of girls with erythrocyanosis crurum puellarum. Application of estrone ointment to the skin had no distinct effect on the cutaneous temperature. It is a question how much of the effect on the temperature was caused by an action on the vegetative nervous system and how much by a central action via hypophysis and ovary. Nothwithstanding the transitory elevation of the cutaneous temperature caused by the estrone preparations, the picture of the patients' illness remained unchanged.

VAN CREVELD, Amsterdam, Netherlands.

HEPATIC CHANGES IN BESNIER-BOECK'S DISEASE; CONTRIBUTION TO THE DIAGNOSIS. F. S. P. VAN BUCHEM and T. BOTMAN, Nederl. tijdschr. v. geneesk. **87**:1643 (Oct. 30-Nov. 6) 1943.

In 6 out of 8 cases of Besnier-Boeck's disease the biopsy specimens from the liver contained the typical epithelioid-cellular tuberculoid foci characteristic of Besnier-Boeck's disease. In the 2 cases in which these structures could not be found, the patients had long shown considerable improvement. The occurrence in

foci makes it possible that the changes may not be observed in the biopsy specimen which involves only a small part of the liver. On the other hand, the characteristics of the tuberculoid foci of the disease often are more pronounced in the liver than elsewhere in the body, a fact which is difficult to explain. Biopsy of the liver must be regarded as an aid in the diagnosis of Besnier-Boeck's disease.

VAN CREVELD, Amsterdam, Netherlands.

Miscellaneous

EXPERIMENTAL AND CLINICAL STUDIES ON THE ACTION OF HIGH DOSES OF HYKINONE AND OTHER MENADIONE DERIVATIVES. RICHARD K. RICHARDS and SHEPARD SHAPIRO, J. Pharmacol. & Exper. Therap. **84**:93 (June) 1945.

Study was made to determine whether large amounts of antihemorrhagic quinones given to promote prothrombin syntheses will exert toxic effects. Such large doses are important in pediatrics to prevent salicylate-induced prothrombopenia.

In man doses approximately ten times as great as those generally recommended for therapeutic use, given daily for a period of one week, induce no significant changes in the blood.

These preparations may be given over long periods of time to man without alteration of the red cells and hemoglobin.

When menadione bisulfite is administered in cases of active rheumatic endocarditis to counteract the prothrombopenia caused by salicylate medication, the blood remains free of toxic changes.

A hepatic function test of high sensitivity is established by the effect of antihemorrhagic quinones in the presence of hepatic disease. By this means it is possible to detect hepatic disturbances in subclinical stages and when the existing prothrombin level is normal.

PILCHER, Cleveland.

SUGGESTIONS FOR A SUCCESSFUL SPEECH CORRECTION PROGRAM IN PUBLIC SCHOOLS. STANLEY AINSWORTH, Quart. J. Speech **31**:471, 1945.

The author gives suggestions for cooperation between speech correctionists of the public schools and the school system.

MARTIN F. PALMER, Wichita, Kan.

CLINICAL CONTRIBUTIONS. P. RUEDA, Arq. de pediat. **15**:7 (Oct.) 1942.

The author reports a case of hypertrophy of the thymus in a girl 1 month and 1 day old, with a clinical picture of dysphagia. The attacks were characterized by cyanosis, ocular convulsions and loss of consciousness. The disease was cured by radium therapy.

Two cases of neuropathic disturbances in infants with vomiting, continuous crying and diarrhea are also reported. Both patients had a successful recovery through the administration of parathyroid extract.

Rueda also mentions a case of bilateral luxation of the hip joint in a girl with a hereditary history of syphilis and with positive reactions to Wassermann and Kahn tests. She improved with arsenical therapy. Another case of congenital atrophy of the left arm and foot in a girl 3 months old is reported. The Wassermann test elicited a positive reaction. An increase of the body weight followed the arsenical therapy.

LOZOYA, México, D. F., Mexico.

Society Transactions

CHICAGO PEDIATRIC SOCIETY AND CHILDREN'S DIVISION OF COOK COUNTY HOSPITAL

Louis W. Sauer, M.D., President, Chicago Pediatric Society
A. H. Parmalee, M.D., Chief of Staff, Children's Division

Joint Meeting, April 16, 1946

Ovarian Agenesis with Dwarfism. Dr. I. P. Bronstein, with Dr. E. Loeffler.

I should like to call attention to a syndrome occurring in adolescent girls characterized by dwarfism and remarkable genital retardation. It is my opinion that the basis for the condition is some type of ovarian agenesis. These patients present either pubic or axillary hair or both. A possible explanation is that the adrenal cortex is responsible for the hair. In addition to ovarian agenesis and dwarfism these patients may present other congenital defects, coarctation of the aorta being one of these. In 1 girl studied both arms presented dyschondroplastic changes as evidenced by roentgenography. Our patient was a Negro girl who came in moribund and died a few days later from an unrelated condition. She was readily recognized as a dwarf, and because of the pubic hair the diagnosis of ovarian agenesis was suggested; the observations at necropsy confirmed this.

Slides were shown of 2 other girls studied. One was given thyroid extract, and an attempt was made to stimulate growth by available products on the market, with little success. Then gonadotropic stimulation was tried with little result. Diethylstilbestrol produced vaginal bleeding and enlargement of the breasts. It is planned to confirm the diagnosis by an exploratory laparotomy.

DISCUSSION

Dr. E. Loeffler: The postmortem examination of this girl confirmed the clinical diagnosis of congenital defect of the ovaries. Another important finding was hyperplasia of the hypophysis with eosinophilia. The cause of death was pneumonia. These cases prove that there is a congenital defect of the ovaries, though the epoophoron and the rete may be present. It is associated with infantilism and dwarfism. The general character of the body is female. The normal development of the rest of the female genitalia is not due to influence of the gonads but is determined genetically.

To explain the dwarfism one could assume that the lack of sex cells or their early degeneration is caused by damage to the genes of the mother or father. Damage to a chromosome or gene has been shown in many cases to cause changes in different parts of the body. It is possible that the same change which causes the aplasia or degeneration of sex cells is also responsible for reducing the genetic height of the subject. The dwarfism of such a person would be genetic and not hormonal.

The observation of a retarded epiphyseal closure seems to contradict this assumption. However, this can be explained as a secondary hormonal event. The inhibitory effect of the sex hormone on the hypophysis is lacking, and in the framework of the genetic dwarfism the growth period is extended.

Cardiac Enlargement in Infants, Simulating Coronary Disease. Dr. B. M. Gasul.

These are 2 cases in the order seen. I was consulted concerning the first baby when it was 5½ months of age, in January 1938, because of its failure to gain

weight, its poor appetite and occasional loose stools, and because it was a "colicky" baby. It had crying spells during and after feeding and would become pale and perspire profusely. The baby was two weeks premature, and otherwise normal. It weighed 17 pounds and 14 ounces (8,108 Gm.) and was 21 inches (53.3 cm.) in height.

The essential observations were that the heart was considerably enlarged but that there was no murmur or cyanosis; the pulse was rapid. The fluoroscope showed the greatest diameter of the heart to be 8.5 cm. and of the chest 12 cm. There were no other signs referable to the heart. Reactions to the blood, urine and tuberculin tests were negative. Pericarditis with effusion was quickly excluded. Tests were performed for glycogenesis, and this was also excluded. Then idiopathic cardiac hypertrophy was considered, and an electrocardiogram was made.

The electrocardiogram showed tachycardia, with a rate of about 160. The T waves in leads I, II and III were inverted; ST 1 and ST 2 were depressed, and there was no axis deviation. The cardiologist, not realizing that the patient was an infant, reported that this was a case of coronary thrombosis. When the literature was checked an exactly similar case was found, reported in 1933 by White and his associates, who saw a baby aged 3 months with an enlarged heart. They found the same electrocardiographic picture. They did not know what it was and did not make a clinical diagnosis. When the baby died they found that the left branch of the coronary artery originated from the pulmonary artery instead of the aorta. They found that 6 other cases had been reported, none of which was diagnosed clinically. They explained the apparent hypertrophy of the heart as a compensatory mechanism. Their review of other cases revealed a characteristic pathologic picture of pronounced myocardial degeneration, in some cases complete replacement by fibrous tissue with resulting aneurysmal dilatation of the ventricular wall. These changes depend on the inadequate nourishment of the ventricular wall by the venous blood and by the low pressure in the pulmonary artery as compared to the aorta.

A considerable bulge in the left ventricle could be seen on one of the slides shown. A clinical diagnosis of this congenital malformation was made, and the slides and electrocardiogram prove that clinical diagnosis is possible. Both Dr. White and Dr. Maude E. Abbott, on viewing the electrocardiograms, agreed with this diagnosis.

In January 1946 a second child was seen, a 3 month old baby delivered by cesarean section, perfectly normal until one day prior to coming under observation, when it had a slight cough and rapid respiration. The apex of the heart was definitely to the left; there was no cyanosis or murmur. Roentgenograms taken at the hospital showed considerable cardiac hypertrophy. When the history of crying spells, especially during feedings, was learned, an electrocardiogram was ordered, but the baby died before this was done. A clinical diagnosis was made that the left branch of the coronary artery came off the pulmonary artery, and this was proved at autopsy.

It is believed that these 2 cases, the first in which clinical diagnosis was made, together with that of Dr. White in which diagnosis was made at autopsy, bring out a definite clinical entity which should be separated from idiopathic cardiac hypertrophy. They are apparently not so rare as one might think. Until Dr. White pointed out the possibility of diagnosis nothing was known about it, but since how to make the diagnosis is now known, many more of these cases will probably be seen.

DISCUSSION

DR. E. LOEFFLER: The postmortem examination confirmed the clinical diagnosis that the left coronary artery originated from the pulmonary artery. The heart was enlarged and there was extensive replacement fibrosis in the myocardium. Thus these cases resemble coronary occlusion.

A second case was posted a few weeks after the first. In this case a clinical diagnosis was not made, as the infant died shortly after admission. The observations were similar.

Though there were 2 cases in succession, this condition is still considered rare, as it could hardly be overlooked at postmortem examination.

Surgery of Patent Ductus Arteriosus. DR. R. W. MC NEALY.

Through the courtesy of the Pediatric Department I have operated on 2 patients with patent ductus arteriosus in the past year. I have been interested in vascular surgery for many years but have not had anything so interesting as this.

In the first case, after the ductus was ligated, a rather soft systolic murmur was noted, which was due probably to a defect in the interventricular septum. The pulmonary artery was extremely enlarged (about the size of a garden hose) and possessed a pronounced expansile pulsation.

The second child had a rather typical patent ductus with apparently no other anomalous condition of the vessels or heart. It had, however, some defect in cerebral development and congenital cataracts. This was unfortunate from the standpoint of surgery because the child made a splendid recovery and the signs and symptoms of patent ductus disappeared.

Leonardo Botallo, an Italian anatomist of the sixteenth century, was the first to describe the persistence of a short vessel in the fetus between the main pulmonary artery and the aorta. The structure now bears his name, as Botallo's duct, duct of Botallo or ductus arteriosus Botalli. In 1907 Munroe, having found this anomaly in a cadaver, thought it offered some possibility for surgical attack. He wrote about it in the *Annals of Surgery* and suggested that it might be successfully ligated. He suggested that it might even be crushed and the circulation interrupted without ligation.

A recent article in *Surgery, Gynecology and Obstetrics* showed a complicated method of occlusion of the ductus arteriosus with a suture ligature. This seemed a laborious method for closure of a simple vessel. I have reservations about whether ligatures will cut through as has been suggested; there is little difficulty with sutures cutting through in ordinary vascular surgery, and why it should do so here I cannot understand. I doubt that this tendency exists. There is this to be said about all ligations of vessels: If vessels are ligated with rather wide ligatures and not tied too tightly, there is every reason to expect that the vessel will be obliterated. However, if the ligature is tied too tightly there is the possibility that it might cut through.

With the presence of the characteristic arteriovenous murmur, a distinct thrill over the base of the heart and enlargement of the conus arteriosus, there is little difficulty in making a diagnosis. However, there may be considerable difficulty in ruling out other cardiac complications which may contraindicate surgical intervention.

When Munroe first suggested operating in these cases he presented a rather clumsy method. He suggested that the sternum be sawed vertically in half and the two sides of the chest be pulled apart. He called attention to the fact that there would be difficulty in getting the thymus out of the way and pointed out that considerable difficulty might be met in trying to approach the concavity of the aortic arch without entering the pericardium. It must be remembered that Munro never performed the operation, but merely attempted to present a possible method.

The suggested approach at present is comparatively easy. I have operated on the heart a number of times, and there is usually no great difficulty encountered.

A flap of pectoral muscle is turned back as far as the posterior axillary line, and a division is made of the third, fourth and fifth costal cartilages. The ribs are then spread apart, and ample exposure is obtained. The approach to the ductus arteriosus is through the left parietal pleura as it passes over the base of the heart, and the route is just anterior to the vagus, between it and the phrenic nerve. Most anatomic illustrations show the ductus almost in the center of the concavity of the aortic arch, but when one approaches it surgically it does not occupy this position. It is found much farther to the left on the descending part of the aorta. One can

be reasonably sure by following the vagus and the left recurrent laryngeal nerve.. The left inferior recurrent laryngeal nerve invariably passes beneath the ductus.

If one does happen to open the pericardial sac, the difficulty is not great. In the second case, I had passed the first ligature easily. With the second ligature the thin pericardial wall was caught on the tip of the forceps and immediately frothy bloody fluid came into the wound. The only thing that was necessary after ligation was aspiration of a small amount of pleural exudate. There was practically no change in the action of the heart and there was no alteration in the child's condition. Recovery was uneventful.

When the cavity in the left side of the chest is entered, the left lung drops out of the way by receding into the back of the chest and does not interfere with the approach to the ductus. At intervals the lungs are inflated under a little positive pressure, and the operation proceeds without difficulty. In ligating the ductus arteriosus I used braided silk and tied it down lightly. The ligature remains as a constant irritant, and I think it unnecessary to place a ligature on each end and likewise inject strong escharotics into the ductus to insure sclerosis. Neither does it seem necessary to suture the severed ductus in this confined area when ligation can be accomplished so easily and should fulfil the need of permanent occlusion.

Progress Report on Treatment of Congenital Syphilis with Penicillin.
Dr. I. Michael Levin.

A year ago I presented before this society a preliminary report (begun in November 1944) on the use of penicillin in the treatment of 25 infants who had congenital syphilis. They were given exacting pediatric care. The diagnosis of syphilis was based on physical observations, roentgen studies and repeated serologic quantitative Kahn tests performed on divided samples by the laboratories of the Chicago Board of Health and the Illinois Department of Public Health. Possible serologic "carry-overs" were ruled out by a period of observation extending over eight weeks. The dosage was 12,500 Oxford units every three hours for eight days, a total of 800,000 units given intramuscularly.

The search for toxic reactions was by clinical observation and laboratory studies, and was conducted along the same lines as in the report on the five day intensive arsenotherapy of congenital and acquired syphilis in infants and children, published in December 1942 in *The Journal of the American Medical Association*. Laboratory studies included determination of nonprotein nitrogen, ascorbic acid, icterus index, total protein, albumin, globulin, calcium, phosphorus and phosphatase; blood counts including counts of platelets, and urinalyses including determination of urobilinogen. Studies of the blood and urine were repeated on the fourth day of treatment; and all studies were duplicated two or three days after the series of injections of penicillin had been completed.

There were no toxic reactions in the first series and no significant changes in the blood or urine. No infant entering without a manifest infection responsible for fever had pyrexia as a result of treatment. On the contrary, the fever usually subsided within twenty-four to forty-eight hours after the inception of penicillin therapy.

The dosage employed was far in excess of that reported in the literature. The special teamwork and critical observation developed in the Cook County Hospital in the massive arsenotherapy employed in the preceding four years made us feel competent to employ this dosage.

The present progress report includes data on 99 infants and children given the same dosage. Sixty-six infants were 4 months old and less, and 16 were between 5 and 12 months of age. There were 7 in the group between 1 and 2 years, and 10 between 2 and 8 years of age. The group of 66 averaged between 4 and 7 pounds (1,814 and 3,175 Gm.) in weight.

Serologic reversal to negative occurred in 40 infants; 36 reversals were in the age groups to 4 months, 3 between 6 and 8 months and 1 in the 1 to 2 year group.

There were 31 patients who have not been observed for a long enough period, but 13 of these have a favorably falling titer.

Seven failed to respond. One was in the 2 month old group and the others in the group between 1 and 8 years old. Of these, 3 had previously been given intensive arsenotherapy unsuccessfully.

Twenty-one patients were not brought back to the clinic for follow-up study.

Reversal of serologic reaction to negative occurred in 27 of 40 infants (67.5 per cent) within five months.

Reversal of serologic reaction has persisted in the 40 patients for periods up to thirteen months. No relapse has occurred as yet.

Of the total series, 47 patients have been adequately observed and of these 40 became negative, a presumptive success of 85 per cent. The infants under 1 year of age showed almost 100 per cent reversal.

One child who showed a rise in temperature was given a different brand of penicillin and promptly became afebrile. There was no instance of localized abscess.

Treatment with penicillin has not been in use long enough to confirm the serologic reversal as indicative of the cure of syphilis. However, the evidence thus far is strikingly favorable. Penicillin therapy has the great advantage of combating the spirochete and other pathogens at the same time. It obviates the long preliminary period of therapy with compounds of heavy metals before arsenotherapy and makes exacting pediatric care much simpler. It has greatly reduced mortality. It is a safe, nontoxic method of therapy.

(The Frances Juvenile Home Association supplied the funds for the social service studies entailed in this work and carried out by Miss Jensen.)

Measles. DR. ARCHIBALD L. HOYNE.

This is a particularly difficult subject to discuss because you are all so thoroughly acquainted with measles. Consequently, I think that I may merely repeat a few well known facts and also tell you something about experience with measles in the Cook County Contagious Disease Hospital during the past three months.

It is known that measles is a worldwide disease and that susceptibility is practically universal after the age of 6 months. Moreover, it may be taken for granted that one attack confers permanent immunity. Those who grow up in large cities seldom reach adult life without having had this infection, but in small towns and country districts there are likely to be a number who escape it. Therefore, when an adult patient with measles arrives in the hospital my colleagues and I assume two things: (1) he has not had measles before and (2) that he was not raised in Chicago.

Most large cities have epidemics at more or less regular intervals. London had an epidemic every two years from 1856 until 1940, the year of the bombing. Just why the anticipated epidemic did not occur in 1940 is not well understood. In Chicago, epidemics of measles seem likely to develop about every three years. Usually during large epidemics a great proportion of all susceptible children are exposed and, consequently, a new "crop" of babies must grow up and reach the "measles age" before another epidemic can occur.

From 1929 to 1938 in Chicago there was no regular period of two or three years between epidemics. The greatest epidemic the city ever had was in 1938, when there were approximately 37,000 cases. The annual number of deaths has usually been few. But during the first World War there were 98,000 cases of measles among American troops and many fatalities, due to the serious complication of bronchopneumonia. However, the death rate has shown a general tendency to decline. Nevertheless, for the first quarter of this year in 9,512 cases of measles there were 13 deaths in Chicago; last year during the first three months there were no deaths.

The high mortality among young children with measles is often spoken of, and so we are proud of the hospital record this year. There were 176 admissions the first three months and only 2 deaths (1.1 per cent). From this it might be

assumed that the disease was particularly mild, whereas actually I think that the opposite was true. Ninety per cent of patients were less than 10 years of age; the two youngest were 5 months old. There were but 12 patients between 6 months and 1 year of age, so that measles under the age of 1 year seems to be rather uncommon in Chicago.

Among the complications in the 176 patients, 45 per cent had bronchopneumonia at the time of admission and 8 per cent had otitis media. Two patients were pregnant and 1 of these was delivered in the hospital at term. The baby was normal and did not have measles or contract measles while in the hospital. There was 1 patient with appendicitis. It is believed that appendicitis with measles is directly related to the disease, because the same type of round cells are found in the appendix as in the throat. One child had a femoral abscess. Several patients had congenital heart disease and other abnormalities, but made good recoveries despite the fact that the attack of measles was severe.

Encephalitis is a complication of special interest. Our 28 cases in 1938 were the largest number reported in any one season up to that time. We have had 10 cases this year. In practically every instance the encephalitis became manifest before the eruption had disappeared, usually on the third or fourth day of the rash. All but 2 of the 10 patients were more than 5 years of age; the oldest was 20 years. One child had paralysis of both legs but recovered from this condition before she left the hospital. There were only 2 patients who did not appear to regain a comparatively complete normal mentality.

Our chief concern is often the prevention of measles. For this purpose gamma globulin has been successful; it is also of value for modification. Nevertheless, convalescent serum, I believe, is best. Of course, neither of these substances confers permanent immunity.

I do not know that penicillin is of special value for uncomplicated measles. If the patient has pneumonia it is well to use it. For the latter, I think the most valuable therapeutic agent is oxygen and, in addition, one of the sulfonamide compounds.

My impression is that convalescent measles serum does not accomplish much in therapy; however, there are some who think otherwise. We have used it many times when treating patients with encephalitis accompanying measles. When caring for a patient with encephalitis it is desirable to do everything which offers hope of being beneficial. To the first 2 patients who came into the hospital this year we gave 200 cc. of convalescent measles serum intravenously, and both died. The third patient was given plasma and recovered. For the fourth patient convalescent serum was not available, and 200 cc. of plasma was given; the patient recovered. From January 1 until this date we have had 12 cases of encephalitis at Cook County Hospital and have lost only 1. We have had only 2 patients whose mental condition has not cleared up; the outcome for these 2 may be doubtful for many months. In 1938, about one third of 28 patients seemed to make complete recovery; one third died and one third had permanent defects. In each case what the course may be is questionable and there has not seemed to be any particular remedy to alter the outcome.

DISCUSSION

QUESTION: I have seen patients with modified measles contract severe measles a number of years later. Is it your feeling that modification gives permanent immunity?

DR. HOYNE: It has been my belief that an attack of measles, even though modified or attenuated, nearly always confers permanent immunity. Nevertheless, I have heard of reports to the contrary.

QUESTION: How often have you seen a second attack of measles shortly after or long after the first attack?

DR. HOYNE: I have never seen one; I still think that a patient may be assumed to be immune after one attack.

QUESTION: At Great Lakes I had charge of the measles ward, and there were a large number of patients, at least 200; 5 had severe measles, were in the hospital for two weeks, were then discharged and came back about six days later with severer attacks.

DR. HOYNE: In California some years ago there were reports of recurrent measles. Until then I had never seen such a case. In the only instance I recall distinctly, the child had a second rash seven or eight days after the first appeared. Koplik spots were present each time. Unless you yourself have seen the patient on both occasions, second attacks of measles should be considered as doubtful.

QUESTION: Would you advocate using sulfonamide compounds or penicillin as a prophylactic measure in cases of moderate or severe disease?

DR. HOYNE: I do not think a great deal of the sulfonamide compounds as prophylactics for anything except meningitis. However, I believe that almost any one would be tempted to give a sulfonamide drug or penicillin or both in cases of moderate or severe measles on the theory that complications might be prevented. Of course, these drugs are always used in treatment of complications.

DR. LEVIN: During the time there has been this epidemic of measles the incubation period has varied considerably, as has the appearance of Koplik's spots. I have seen 2 cases of encephalitis this year, with the largest number of Koplik spots I have ever seen. I thought that there was complete exfoliation of the mouth. The encephalitis occurred five or six days after onset of the eruption, and after the initial period of lethargy and sleep the patients had periods of tremendous excitement, and recovered. Dr. Levinson said that he had seen 5 patients in private practice, 1 with pronounced neurologic manifestations. Have you seen any cases of hemorrhagic measles?

DR. HOYNE: I think that physicians are inclined to use the term "hemorrhagic" to denote a severer type of rash. In reality, hemorrhagic measles should mean something more, as hemorrhage from the nose, mouth and bowels. Such cases are extremely rare. Other conditions not seen so often are stomatitis and marked cervical adenitis. But the percentage with pneumonia and encephalitis seems to be on the increase. Ordinarily, 1 case of encephalitis is expected in 1,000 cases of measles. Among our 176 patients with measles there were 14 under 1 year of age, with no deaths. Although this is the period of life at which measles is so dreaded, I do not think that the attacks are so seyere at that time as later.

QUESTION: What is the youngest patient you have seen with measles? I saw 1 child 3½ weeks old, brought from a home where the older girl had measles; the baby had measles at the age of 14 days.

DR. HOYNE: We had one somewhat similar instance. A pregnant woman who had never had measles contracted the disease from one of her children at about the time of delivery. When the baby was 3 weeks old it was admitted to the hospital with a rash suggestive of measles.

Book Reviews

Medical Services by Government: Local, State and Federal. By Bernhard J. Stern, Ph.D. Price, $1.50. Pp. 406, with 14 tables in text and 3 tables in appendix. New York: Commonwealth Fund, 1946.

This is one of the Studies of the Committee on Medicine and the Changing Order of the New York Academy of Medicine, established in 1942 to inquire into economic and social problems confronting the medical profession today.

Public medical care has been traditionally identified with the dispensing of relief to the destitute. The "Old Poor Laws" which spring from the Elizabethan "Poor Laws" of 1601, and which became the "Town Poor Relief System" in New England, largely dominate distribution of such services.

Dr. Stern goes into the historical background of medical services and finds that new patterns are emerging which are transforming the field of government medical care. In the chapter "Medical Service by Local Government, Recent Development" the author outlines, after quoting the Resolution of the American Medical Association of 1938 on Medical Care for the Indigent, the various methods of giving such care and the methods employed in organizing physicians to provide public medical services and home and hospital care. The importance of integration of home and institutional care to insure continuity of service is pointed out. The role of the full time health department as the agency shouldering the responsibility of medical care of indigent persons is clearly stated.

School medical services, medical care in jails and needs from the local standpoint are included.

The responsibility of the state is covered in a discussion of diseases which present an element of public danger or involve highly specialized care and high costs. Included in these groups are syphilis, cancer, mental diseases and tuberculosis. Laboratory services and workmen's compensation are also dealt with at this point.

A chapter is given over to the nature and extent of hospital services by government and to information covering tuberculosis, mental and community institutions. The author discusses federal grants-in-aid for medical care, giving the historical background as well as information about the Social Security Act and the Crippled Children, Maternal and Infant Care Program, Vocational Rehabilitation and Tuberculosis and Venereal Disease Control.

Medical services by the Federal Government go back traditionally to the providing of direct medical services to seamen, and it has extended into many other wider fields. There are now programs of medical care for veterans and medical services for rural groups, and medical services are provided through many emergency agencies. Federal agencies directing the major programs are the United States Public Health Service, the Farm Security Agency, the Veterans' Administration and the Medical Corps of the Army and Navy.

The book contains a wealth of factual data about the cost and extent of medical care given, as well as complete references at the end of each chapter.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: New York. Time: Sept. 16-19, 1947.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilsón, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff and Dr. Donald Paterson, Hospital for Sick Children, Great Ormond St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaas Bolwerk 14, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Lyccumplein 10, den Haag.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Ernesto Trigo Pizarro.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: La Paz, Bolivia.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado, 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedas y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Luis Berlanga Berumen, Bucareli No. 85, Altos, Mexico.
Secretary: Dr. Jésus Alvarez de los Cobos, Ignacio Mariscal 124, Mexico.

SOCIEDAD DE PEDIATRIA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba. Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel William Penn, Pittsburgh. Time: Nov. 13-16, 1946.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Mitchell I. Rubin, 219 Bryant St., Buffalo 9, N. Y.
Secretary: Dr. Robert F. Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Wesley H. Anderson, 2404 Washington Blvd., Ogden, Utah.
Secretary-Treasurer: Dr. F. M. Kriete, State Capitol, Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. George Kimmel, Redwing, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver 2.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Stewart H. Welch, 117 S. 20th St., Birmingham 5, Ala.
Secretary: Dr. W. Ambrose McGee, 1601 Monument Ave., Richmond 20, Va.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

ARIZONA PEDIATRIC SOCIETY

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Councill Rudolph, 103–5th St. S., St. Petersburg.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. David Gaberman, 1179 Allyn St., Hartford, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.

Louisiana State Pediatric Society

President: Dr. S. George Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Orleans 15.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Paul N. Morrow, 1614 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellview, Memphis.
Secretary-Treasurer: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Walter Levy, 12 E. 88th St., New York.
Secretary: Dr. Joseph Blasenstein, 960 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Lambert Krahulik, 14 Sidney Pl., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, May and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Joseph Greengard, 4753 Broadway, Chicago 40.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. O. René Caillet, 4325 Cole Ave., Dallas, Texas.
Secretary-Treasurer: Dorothy Wyvell, Bradford Memorial Hospital for Babies, Texas.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Albert L. Hill, 1401 S. Hope St., Los Angeles.
Secretary-Treasurer: Dr. Robert Simonds, 1925 Wilshire Blvd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.
Place: Memphis Country Club. Time: 8 p. m., Dec. 13, 1946.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. R. P. Showalter, 411 E. Mason St., Milwaukee 2.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Secretary: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Jeanne McKinnon-Shofstall, 1019 N. Lee St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Waldo E. Nelson, Temple University School of Medicine, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and April.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

Seattle Pediatric Society

President: Dr. Norman W. Murphy, 1300 Madison St., Seattle 4.
Secretary: Dr. David M. Harris, 630 Medical Arts Bldg., Seattle 1.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.
Secretary: Dr. H. M. Van Dyke, 541 E. Broadway, Long Beach, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.
Place: University Hospital, Ann Arbor, Mich. Time: Oct. 25-26, 1946.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.